Association between high body mass index and adverse birth outcomes by HIV and ART status in Cape Town, South Africa

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PREAMBLE

DECLARATION

I, **Hlengiwe Pretty Madlala**, hereby declare that the work on which this dissertation is based is my original work (except where acknowledgements indicate otherwise) and that neither the whole work nor any part of it has been, is being, or is to be submitted for another degree in this or any other university. I further declare that this work was not published prior to my registration for the degree of Master of Public Health (Epidemiology and Biostatistics).

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ABSTRACT

Background: Tested independently, studies report that obesity and HIV infection and/or ART use in pregnancy are associated with adverse birth outcomes. However, there is limited data on the combined impact of these maternal factors on adverse birth outcomes. Given the high prevalence of obesity and HIV infection in Sub-Saharan Africa (SSA), understanding these associations is important. This study examined the association of the double burden of high maternal body mass index and HIV infection/ART use in pregnancy with adverse birth outcomes.

Methods: Part A of this mini-dissertation presents the study protocol which outlines the rationale, aim and objectives of the study; the research methodology, analysis plan and ethical considerations. Part B is the literature review of studies conducted in SSA which investigated the relationship between BMI and HIV infection and adverse birth outcomes of interest. Part C is the journal-formatted manuscript which presents the results and discussion of the study findings in relation to other scholars. The referencing style used for the whole thesis is Vancouver as required by the journal chosen for the formatting of the manuscript.

We used data collected from a large observational Prematurity Study that enrolled HIV-infected and HIV-uninfected women seeking antenatal care at Gugulethu MOU in Cape Town between April 2015 and October 2016. A subset of HIV-infected women who booked early (≤24weeks) was prospectively followed through delivery and was used to study gestational weight gain (GWG) and adverse birth outcomes. Data was obtained from review of medical records and study questionnaires. Logistic regression was used to compare birth outcomes by BMI status: preterm delivery (PTD), low/high birthweight (LBW/HBW) and small/large gestational age (SGA/LGA) between HIV-uninfected and -infected women; and between HIV-infected women who initiated ART before pregnancy and those who initiated ART during pregnancy. Using the subset of HIV-infected women who booked early (≤24weeks), we compared the adverse birth outcomes between low, adequate and high GWG.

Results: Of the 2779 participants included in the analysis, 20% had normal BMI, 29% were overweight, 51% were obese and 39% were HIV-infected. Overall, there was no association between obese BMI and PTD (aOR 1.06, 95% CI 0.75-1.49). Instead, obese BMI was negatively associated with LBW (aOR 0.53; CI: 0.39-0.72) and SGA infants (aOR 0.55, 95% CI 0.41-0.75) compared to normal BMI women. Stratifying by HIV infection showed similar

results for LBW (aOR 0.54; CI: 0.35-0.83) and SGA (aOR 0.60, 95% CI 0.38-0.94) in obese HIV-infected women compared to corresponding women with normal BMI. However, comparison of obese HIV-uninfected and obese HIV-infected women showed a higher incidence of LBW and SGA infants in obese HIV-infected women (12% vs 8%). The association of obese BMI and LBW and SGA in HIV-infected women did not differ by timing of ART initiation.

In terms of HBW and LGA, overall, obese BMI was positively associated with HBW (aOR 2.00; CI: 1.13-3.57) and LGA infants (aOR 1.98, 95% CI 1.40-2.80) compared to normal BMI women. Stratifying by HIV infection also showed a positive association between obese BMI and HBW (aOR 2.54; CI: 1.17-5.53) and LGA (aOR 2.30; CI: 1.46-3.62) in HIV-uninfected women. Although a similar positive association was also obtained in obese HIV-infected women, the strength of this association was weaker for both HBW (aOR 1.41; CI: 0.59-3.34) and LGA (aOR 1.58; CI: 0.91-2.72). When the analysis was restricted to HIV-infected women by timing of ART initiation we found that obese women who initiated ART during pregnancy had 3-fold likelihood of having LGA infants (aOR 3.26; CI: 1.32-8.09) and those who initiated ART before pregnancy had a reversed effect (aOR 0.87; CI: 0.43-1.78) compared to respective normal BMI women. However, restricting the analysis to obese HIV-infected women only revealed a counter effect of the two conditions where the frequencies of both LGA and SGA are high. Abnormal gestational weight gain had no association with PTD, LBW, HBW and SGA. However, we showed that GWG lower than the IOM recommended values reduced the likelihood of having LGA infants (aOR 0.29; CI: 0.12-0.70) compared to adequate GWG.

Conclusions: Obese HIV-infected women appear to be cushioned by their BMI against LBW and SGA when compared to normal BMI. However, comparison of these outcomes amongst women who are either obese or HIV-infected reveal a higher burden of both SGA and LGA infants in obese HIV-infected women, regardless of ART initiation status.

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LIST OF ABBREVIATIONS

AGA	Appropriate for Gestational Age
ANC	Antenatal Care
aOR	Adjusted Odds Ratio
ART	Antiretroviral Therapy
BMI	Body Mass Index
BMJ	British Medical Journal
CI	Confidence Intervals
CRF	Case Report Form
GA	Gestation Age
GWG	Gestational Weight Gain
HAART	Highly Active Antiretroviral Therapy
HBW	High Birthweight
HIV	Human Immunodeficiency Virus
HPTN	HIV Prevention Trial Network
HREC	Health Sciences Research Ethics Committee
IGF-1	Insulin-like Growth Factor-1
IL-6	Interleukin-6
TNF-α	Tumour Necrosis Factor-α
IOM	Institute of Medicine
IUGR	Intrauterine Growth Restriction
LBW	Low Birth Weight
LGA	Large for Gestational Age
LMP	Last Menstrual Period
MCR	Maternity Case Record
MI	Medically Indicated
MOU	Maternity Obstetric Unit
NCD	Non-Communicable Diseases
NIH	National Institutes of Health
NVP	Nevirapine

PIMS	Prematurity Immunology in Mothers and their Infants
PMTCT	Prevention of Mother-to-Child-Transmission
PROM	Premature Rupturing of Membranes
PTD	Preterm Delivery
RCT	Randomized Controlled Trial
SDG	Sustainable Development Goal
SFH	Symphysis-Fundal Height
SGA	Small for Gestational
SSA	Sub-Saharan Africa
UCT	University of Cape Town
US	Ultrasonography
UTT	Universal Test and Treat
WHO	World Health Organisation

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PART A: RESEARCH PROTOCOL

1. INTRODUCTION

1.1 Background

Over the years, there has been a growing concern regarding the increasing global prevalence of obesity. Obesity is a risk factor for type II diabetes, hypertension, heart disease and some cancers (1, 2). Ironically, there is a belief that overweight and obesity prevalence is highest in developed countries due to consumption of Western foods rich in fat/sugar and increased sedentary lifestyle (3). However, it is developing countries that have doubled the burden of chronic non-communicable diseases due to upward shift in obesity prevalence, particularly in Africa (4). Body fat is estimated by body mass index (BMI) which is individual's weight in relation to their squared height. Standard BMI classification by the World Health Organisation (WHO) include underweight (≤18.5 kg/m^2), normal weight (18.5-24.9 kg/m^2), overweight (25-29.9 kg/m^2) and obese (≥30 kg/m^2) people (5).

The Demographic and Health Survey reported that South Africa is the most obese region in Sub-Saharan Africa (SSA) with approximately 68% women being either overweight or obese, and one in five being severely obese (BMI ≥35.0 kg/m^2) (6). As a result, most women reach their reproductive age (15 - 49 years) with high BMI (defined as either overweight or obesity). In pregnancy, women tend to further gain weight due to overeating and foetus weight; this is known as gestational weight gain (GWG). Recent studies show that women with high pre-pregnancy BMI are likely to have increased GWG compared to those who have normal weight; and both these factors have adverse maternal and infant health outcomes (7, 8). For this reason, the Institute of Medicine (IOM) came up with recommended ranges for GWG based on WHO BMI categories (Table 1) to allow monitoring of weight gain during pregnancy by health practitioners to identify women at high risk for adverse health outcomes (9, 10).

Table 1. Institute of Medicine gestational weight gain guidelines (9)

Pre-pregnancy BMI	**Total weight gain**
Underweight (<18.5 kg/m^2)	12.5 – 18 kg
Normal weight (18.5 – 24.9 kg/m^2)	11.5 – 16 kg
Overweight (25.0 – 29.9 kg/m^2)	7 – 11.5 kg
Obese (≥30.0 kg/m^2)	5 – 9 kg

The table above shows the WHO classification of BMI categories from underweight to obese individuals, next to each BMI category is the IOM recommended weight gain during the entire pregnancy period. For example, people who are in the overweight category should only gain an additional total weight of 7-11.5 kg during pregnancy, if they fail to reach or if they exceed this range, they will be at high risk of adverse pregnancy and birth outcomes (9).

In addition to being the most obese region in SSA, South Africa has the highest prevalence of human immunodeficiency virus (HIV) infection. Similar to high BMI burden, the majority of adults living with HIV infection are women aged between 18-30 years, an age range that coincides with their peak reproductive years (11). Maternal HIV infection and long-term use of antiretroviral therapy (ART) during pregnancy have been reported to be associated with an increased risk of adverse birth outcomes (12-16). HIV infection and ART-related adverse birth outcomes include preterm delivery (PTD), low birth weight (LBW) and small size for gestational age (SGA) infants (13-17).

Similarly, the specific birth outcomes associated with high BMI and GWG that have been interrogated in the literature include PTD, LBW (18-20) and other outcomes such as high birthweight (HBW) also known as macrosomia (birthweight >4kg) (21, 22), intrauterine growth restriction (IUGR), caesarean section delivery (23), preterm rupture of membranes, post-term births (24), stillbirth, miscarriage, large for gestational age (LGA) infants, Apgar score of <7 at 5 minutes, neonatal intensive care admissions, early neonatal death and congenital abnormalities (22, 25-27).

Preterm delivery is the leading cause of neonatal mortality and morbidity worldwide (28). Although some studies have reported a protective effect of maternal BMI against PTD (29, 30), others suggests that high BMI increases PTD via intrapartum complications such as pre-eclampsia, gestational diabetes and hypertension (19, 31). On the other hand, HIV infection and/or ART use are said to mediate PTD via systemic immune activation and inflammation (32-34). With the increasing number of women being initiated on ART in pregnancy due to WHO universal test and treat (UTT) guidelines (35), the consequences of the combination of long-term ART use and high BMI on maternal and child health are currently not clear. Therefore, quantification of harmful effects of obesity in pregnant women using ART is of public health importance in our setting.

1.2 Rationale

Obesity is a growing public health concern because of the increased number of women who reach childbearing age with high BMI. Data from high income countries has shown that high BMI is associated with adverse birth outcomes. In Africa, there is growing evidence sharing the association between ART use in pregnancy and adverse birth outcomes, resulting in long-term child morbidity (15, 16, 36). Given the high prevalence of both obesity and HIV infection in women of child-bearing age, it is important to investigate the combined association of these factors in pregnant women. In South Africa, a preliminary analysis of a study conducted in Gugulethu on adverse birth outcomes has shown that there is high prevalence of obesity among HIV-infected women seeking antenatal care (ANC). However, the influence of this observation on birth outcomes has not been analysed. Therefore, this study will investigate the association of high BMI and GWG with adverse birth outcomes by HIV status and timing of ART initiation in this cohort. The specific outcomes of interest are PTD, LBW, HBW, SGA and LGA.

2. AIM AND OBJECTIVES

2.1 Aim

The aim of this study is to examine the association between high BMI (overweight and obese) and gestational weight gain (GWG) and adverse birth outcomes in women seeking antenatal care (ANC) at Gugulethu Maternity Obstetric Unit (MOU) in Cape Town, South Africa.

2.2 Objectives

- To describe the prevalence of high BMI among pregnant women seeking ANC;
- To examine the association between high BMI at first ANC booking and adverse birth outcomes by HIV and ART status; and
- To examine the association between gestational weight gain (GWG) and adverse birth outcomes in a subset of HIV-infected women who booked early (≤ 24 weeks).

3. METHODOLOGY

3.1 Study Design

This study will be a secondary data analysis of data collected from a large observational cohort titled: “The Prematurity Immunology in HIV-infected Mothers and their infants Study (PIMS)". The overall aim of the parent study is to quantify the association between ART use in pregnancy and adverse birth outcomes in Cape Town, South Africa. The overall cohort of the parent study

includes all women booking for their first ANC between April 2015 and October 2016. A subset of these women, who booked early (≤24weeks) and were HIV-infected were enrolled into a prospective cohort study with intensive measurement through pregnancy to 12-month postpartum period.

3.2 Study Setting

This study is taking place in the Gugulethu community, which has a population of approximately 98 468 residents (37). The residents of Gugulethu are predominantly of a low socioeconomic status with an average monthly income of ≤R3 200 (37). The Gugulethu MOU serves this population by providing antenatal, obstetric and infant care for low risk pregnancies to approximately 5 000 women per annum. Women with history of pregnancy complications or who require specialist care are referred to secondary (Mowbray Maternity Hospital) or tertiary (Groote Schuur Hospital) level obstetric facilities. This is particularly important for this current study as high BMI and GWG is associated with pregnancy complications which could require deliveries in these facilities.

3.3 Study Population and Sampling

A total of 3 254 pregnant women aged 18 years and above were enrolled into the parent study between April 2015 and October 2016. A subset of 550 women who booked early (≤24 weeks) were enrolled into the prospective cohort.

3.4 Data Collection

3.4.1 Exposures of Interest

For maternal BMI, data will be abstracted into the study form (Appendix 4B) from the maternity case records (MCR) as weight and height measurements are performed routinely by clinic nurses in all women attending their first ANC. Baseline BMI will be calculated as weight divided by the square of height. The limitation of not having pre-pregnancy BMI will be corrected by adjusting for length of gestation at first booking in the analysis (38, 39). For the first comparison (Assessment A), BMI will be categorised based on WHO standards:

- Normal BMI (18.5-24.9 kg/m^2)
- Overweight (25-29.9 kg/m^2)
- Obese (≥30 kg/m^2)

For maternal GWG, data will be obtained from study case report forms (CRFs) as weight measurements are performed by trained study personnel during the follow-up period of ≤24 weeks to 12 months post-partum (Appendix 4D). Total GWG will be calculated as the difference in the weight obtained from the third trimester visit and weight at enrolment. For the second comparison (Assessment B), GWG will be categorised based on IOM standards as shown in (Table 1):

- Low (< IOM)
- Adequate GWG (= IOM)
- High GWG (>IOM)

The information regarding HIV/ART status will be obtained from the MCR study form (Appendix 4B) and will be categorised as:

- ART initiated before pregnancy
- ART initiated during pregnancy

3.4.2 Outcomes of Interest

For adverse birth outcomes, obstetric data will be collected into the obstetric study form (Appendix 4C) from MCR and from infant clinic card (Appendix 4E) for the prospective cohort participants.

- Gestational age (GA) at delivery

Gestational age at delivery will be categorized into term (≥37) and PTD (<37 weeks).

- Birth weight

Birthweight will be categorized into low (<2500g), normal (2500 - 3999g) and high birth weight (≥4000g).

- Size for gestational age

Size for gestational age will be categorized into small (SGA: <10^{th} percentile), appropriate (AGA: 10-90^{th} percentile) and large (LGA: >90^{th} percentile) for gestational age infants based on INTERGROWTH-21^{st} Project Standards (40, 41)**.**

All the exposure and outcome variables to be included in the analysis are shown in table 2 below.

Table 2. Variables to be included in the analysis

Variable	Scale	Categories
Maternal		
Age (years)	Numerical – continuous	Mean/median
	Categorical – ordinal	<20, 20-24, 25-29, 30-34, ≥35
Height (cm)	Numerical – continuous	Mean/median
	Categorical – ordinal	<155, 156-161, ≥162
BMI	Numerical – continuous	Mean/median
	Categorical – ordinal	Normal, Overweight, Obese
In a relationship	Categorical – binary	Yes, No
Completed High School	Categorical – binary	Yes, No
GA at enrolment	Numerical – continuous	Mean/median
	Categorical – ordinal	1^{st}, 2^{nd}, 3^{rd} trimester
Parity	Numerical – continuous	Mean/median
	Categorical – ordinal	1, 2, ≥3
Gravidity	Numerical – continuous	Mean/median
	Categorical – ordinal	0, 1, ≥2
Total GWG	Numerical – continuous	Mean/median
	Categorical – ordinal	Low, adequate and high
HIV status	Categorical – binary	HIV-infected, HIV-uninfected
ART status	Categorical – binary	ART initiation before and during pregnancy
Infant		
GA at delivery (weeks)	Categorical – binary	Term (≥37), PTD (<37)
Birth weight (g)	Numerical – continuous	Mean/median
	Categorical – ordinal	Low (<2500), normal (2500 - 3999g), high (≥4000g)
Size for gestational age	Categorical – ordinal	Small (SGA), appropriate (AGA), large (LGA)

3.5 Data Management and Analysis Plan

3.5.1 Data Safety

The data collected from the parent study is captured into Microsoft Access database, has automated daily backups to prevent loss and is password protected. Password protection ensures that access to the participant information is restricted to the data manager, principal investigator and study coordinator. The file does not have participant names but only study participant numbers as identifiers.

3.5.2 Data Analysis

All data will be analysed using STATA Version 14 (Stata Corporation, College Station, Texas USA). Continuous variables will be summarised using means/standard deviation (SD) or median/interquartile based on normality distribution. Categorical variables will be summarised using counts/proportions. Statistical significance ($p<0.05$) between groups (BMI: normal, overweight and obesity; GWG: low, adequate and high) will be determined using Chi-squared or Kruskal Wallis test.

To assess the association of high BMI and GWG with adverse birth outcomes, multivariable logistic regression models will be fitted against each of the outcomes of interest using WHO normal BMI and IOM adequate weight gain as reference values. The analysis will first be conducted in the whole sample, then will be stratified by HIV status and further by ART status. All results will be presented as adjusted Odds Ratios (aOR) with 95% confidence intervals (CI). Models will be adjusted for potential confounders identified *a priori* including maternal age, GA at enrolment, parity, gravidity and prior PTD (42).

4. ETHICAL CONSIDERATIONS

The parent study was approved by the University of Cape Town Faculty of Health Sciences Research Ethics Committee (UCT-HREC) (739/2014) (Appendix 2B) and the University of Southampton Institutional Review Board (12542 PIMS) (Appendix 2C). Ethical approval for this proposed study will be sought from the UCT-HREC.

4.1 Informed Consent

Informed consent for the parent study was obtained from the participants prior to enrolment; additional consent regarding access to participant clinical records was also obtained (Appendix

3A and 3B). This study will use the consented data and therefore does not require additional consent from the participants.

4.2 Privacy and Confidentiality

To ensure confidentiality, participants are assigned a 5-digit identifier number which is used in all study documents. Participant folders are kept in locked cabinets to restrict access. The electronic data is password-protected and only the data manager, principal investigator and study coordinator have access to this information. This proposed study will use the original participant identifiers from the parent study and the results obtained will be reported as an average to ensure confidentiality.

4.3 Risks and Benefits

There are no particular risks posed by this study except for the provision of sometimes sensitive information of which is still protected because there is no use of participant names on the CRFs. There are no direct benefits of this study to participants except that they have access to study ultrasound and are given a transfer letter to relevant physician if there are any medical concerns regarding maternal or infant health. Over long term, there will be indirect benefit of improving maternal and child health outcomes in Cape Town. For example, the results of the current study will give an insight into the association of high BMI and GWG with birth outcomes by HIV and ART status, and relevant recommendations will be made available to the Gugulethu Community health centre management.

4.4 Reporting and Implementation

Study findings will be reported in a manuscript that will be submitted in peer-reviewed journal which will be approved by all study stakeholders. Data will also be presented in local and international conferences, meetings, workshops and to the management of the Gugulethu MOU.

4.5 Logistics

Table 3. Study Timeline

Activity	Time (months)				
	Mar-Apr 18	**May-Jun 18**	**Jul-Aug 18**	**Sept 18**	**Oct 18**
Protocol submission to Ethics					
Merge and clean data					
Data analysis					
Thesis and manuscript write-up					
Finalise thesis and submit for marking					
Submit manuscript for publication					

4.6 Budget

Data analysis will be conducted as part of an MPH degree and no payment for the student is required.

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PART B: LITERATURE REVIEW

1. INTRODUCTION

Currently, approximately 7 000 new-born infants die every day, contributing to 46% of all under-5 child mortality (1). The majority of neonatal deaths are due to direct and indirect complications of PTD and SGA births which are both associated with LBW (2). Despite a significant reduction of new-born mortality due to the prioritisation of child health by global health agencies in year 2000, South Africa and other low-middle income countries failed to meet the required target of two-third reduction in 2015 (3). After 2015, the new sustainable development goals (SGD) to be achieved by 2030 were set, goal 3 aims to 'Ensure healthy lives and promote well-being for all at all ages'; including a specific target of reducing the neonatal mortality rate to 12 deaths per 1 000 live births (4). Therefore, to achieve this goal, accelerated efforts are required; especially in SSA where reductions have been slower.

Adverse maternal health is directly responsible for poor child health outcomes. A study conducted by Slyker at al.(5) in Kenyan women found that poor maternal health is associated with PTD, SGA and LBW infants, resulting in 6-fold increased risk of neonatal death. Consequently, any interventions targeting maternal risk factors for these causes of neonatal death can have significant impact in improving neonatal health. One preventable maternal risk factor that can be targeted, due to it's contribution on adverse birth outcomes is obesity, which is on the rise in SSA.

Worldwide obesity prevalence has almost tripled since 1975 (6). In 2016, there were approximately 1.9 billion overweight and 650 million obese adults, with women being the majority compared to males (6). In South Africa, an alarming 68% of women of child-bearing age are overweight or obese (7). This is partly attributed to changing lifestyle from consumption of traditional foods to high fat and high sugar diet, accompanied by increased sedentary lifestyle (8-10). In addition, body weight perception and cultural beliefs of regarding chubby weight as being attractive among women in SSA is reported to be one of the strongest predictors of overweight and obesity (10, 11).

Conflicting evidence exists regarding the association between high pregnancy BMI and adverse birth outcomes. Some studies report PTD, increased birth weight/macrosomia (≥4 kg) and LGA infants (12-14). Whereas, others report LBW and SGA infants due to intrauterine foetal growth restriction resulting from materno-foetal hypoperfusion in obese women (15-17). Other mechanisms implicated in weight-induced adverse birth outcomes are related to maternal

complications such as gestational hypertension, diabetes, pre-eclampsia, thromboembolism and urinary tract infections (18-21).

Similar to high pregnancy BMI, HIV infection without treatment has been shown to be associated with adverse birth outcomes such as PTD, SGA and LBW infants (22-24). However, despite the availability of treatment, the previously observed adverse birth outcomes in women with untreated HIV infection persisted in women receiving treatment (25-28). Therefore, countries with a high burden of HIV/ART-use and obesity will be hindered from achieving the SDG3 target of reducing neonatal mortality rate to 12 deaths per 1 000 live births by 2030 (4). Although there is vast evidence on independent association of obesity with adverse birth outcomes; and of HIV infection and ART-use with adverse birth outcomes, there is limited data regarding the combined impact of both obesity and HIV on birth outcomes. Given the high prevalence of both HIV and obesity in SSA, it is critical to establish whether the combined association exists.

2. AIM AND OBJECTIVES

The aim of this literature review is to explore, appraise and synthesise literature on the association between high pregnancy BMI and adverse birth outcomes in HIV-infected women in SSA. Therefore, this review will focus on selected studies from SSA to identify gaps in the literature that require further research. However, data regarding the exposure and outcomes of interest will also be drawn from high income countries as obesity is a global public health concern.

3. SEARCH METHOD

Relevant articles were searched on online databases including PubMed, MEDLINE, EMBASE and EBSCO platform. Reference list of relevant articles and a general internet search was also conducted to identify more literature and reports from the global health agencies such as the WHO and IOM. The search key words used were a combination of obesity, gestational weight gain, adverse birth outcomes and HIV infection; together with their MeSH terms as shown below:

- *Obesity OR body mass index OR gestational weight change*

  AND

- *Birth outcomes OR pregnancy outcomes*

AND

- *HIV-infected OR antiretroviral therapy*

("obesity"[MeSH Terms] OR "obesity"[All Fields]) OR ("body mass index"[MeSH Terms] OR ("body"[All Fields] AND "mass"[All Fields] AND "index"[All Fields]) OR "body mass index"[All Fields]) OR (gestational[All Fields] AND ("body weight changes"[MeSH Terms] OR ("body"[All Fields] AND "weight"[All Fields] AND "changes"[All Fields]) OR "body weight changes"[All Fields] OR ("weight"[All Fields] AND "change"[All Fields]) OR "weight change"[All Fields])) AND (("parturition"[MeSH Terms] OR "parturition"[All Fields] OR "birth"[All Fields]) AND outcomes[All Fields]) OR ("pregnancy outcome"[MeSH Terms] OR ("pregnancy"[All Fields] AND "outcome"[All Fields]) OR "pregnancy outcome"[All Fields] OR ("pregnancy"[All Fields] AND "outcomes"[All Fields]) OR "pregnancy outcomes"[All Fields]) AND (antiretroviral[All Fields] AND ("therapy"[Subheading] OR "therapy"[All Fields] OR "therapeutics"[MeSH Terms] OR "therapeutics"[All Fields])) OR hiv-infected[All Fields]

3.1 Inclusion and Exclusion Criteria

The search was restricted to publications written in English. Only studies conducted in SSA were included for the review. Due to limited number of articles retrieved, there was no restriction on the publication or data collection years. The literature that was found relevant was published between years 1999 and 2018, and data was collected between 1992 and 2016. All study designs were included, the population of interest was HIV-infected (treated or untreated) and -uninfected pregnant adult women. The exposure of interest was pregnancy BMI and/or GWG; studies with either PTD, birth weight or size for gestational age as an outcome were included. All included studies are summarised in Tables 1a.

4. QUALITY AND COMPARABILITY OF STUDIES

A total of 357 articles were retrieved during the search of PubMed, MEDLINE, EMBASE and EBSCO platform. Following the screening of titles and abstracts, 132 articles were deemed irrelevant for the review because they did not have the three factors that this study is assessing; they either examined association between obesity and adverse birth outcomes or between ART-use and adverse birth outcomes and not the combination of both exposures. After screening the methodology and full text of the remaining articles, 214 of them were excluded for various

reasons including irrelevant population, not conducted in SSA and absence of relevant comparison groups (Figure 1), leaving a total of 9 included articles from PubMed (22, 24, 29-35). One additional article was obtained from review of reference lists of relevant publications (23) and 2 MMed theses were retrieved from EBSCO platform (36, 37), making a total of 12 reviewed studies. The quality and comparability of all 12 studies was assessed based on study design, sample size and outcome assessment method as summarised in Table 1a and 1b.

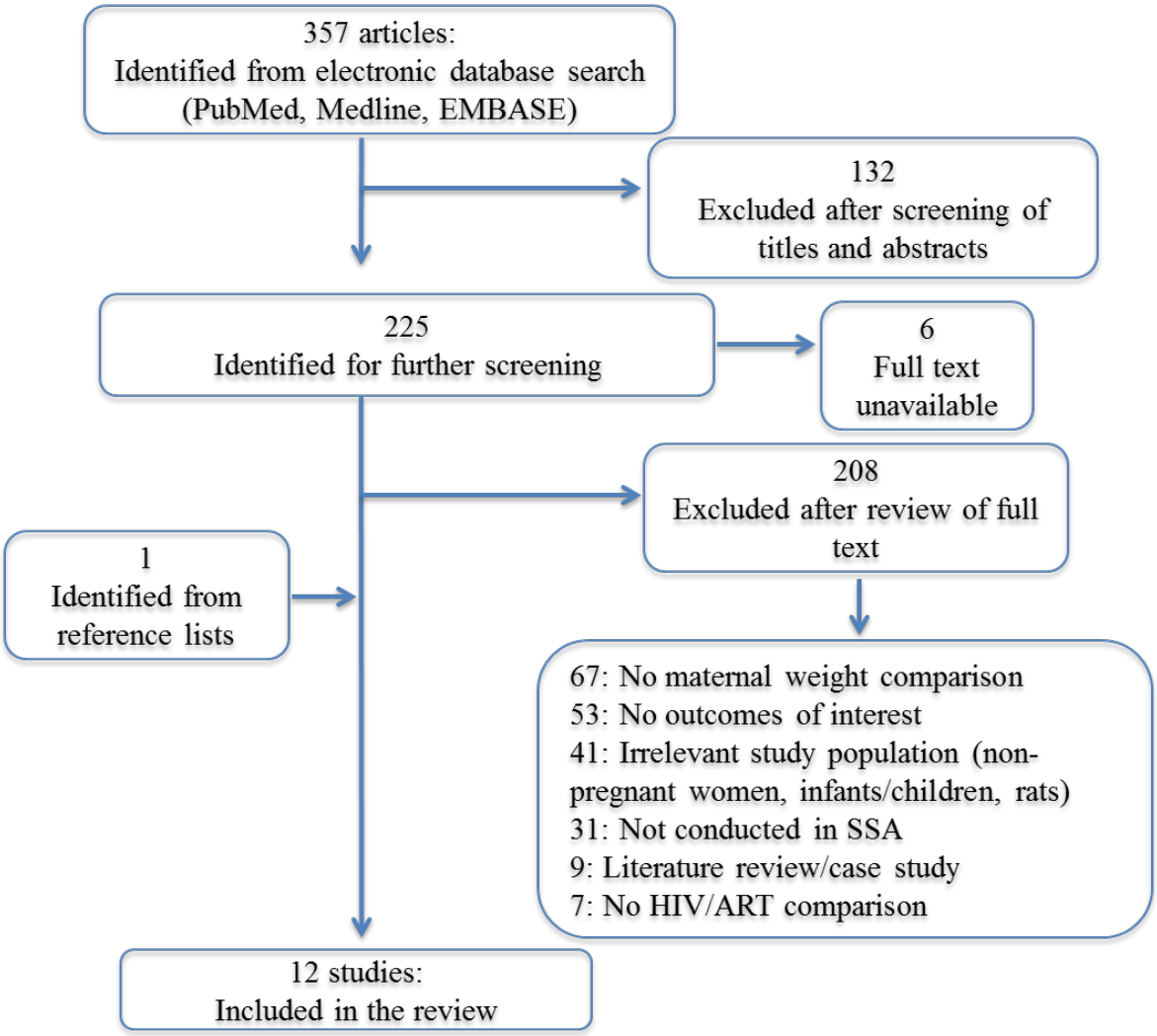

Figure 1. Flow diagram showing the selection process for the reviewed studies

4.1 Study Design

Out of the 12 eligible studies included in the review, 6 of them were observational cohort studies and the other 6 studies were randomized controlled trials (RCTs). Four out of the 6 observational studies had prospective follow-up and were conducted in Rwanda, South Africa and Zambia (23, 29, 32, 36). These 4 studies enrolled participants at first trimester (<28 weeks

GA) (29, 32), second trimester (>28 weeks GA) (23) and during labour (36). Three out of the 4 studies collected the exposure and outcome data from study measures such as questionnaires, anthropometric measurements and laboratory testing of collected specimens during different study visits (23, 29, 32). The other study used a combination of both study measures and abstraction of information from clinical records (36). The remaining 2 out of 6 observational studies had retrospective follow-up and were conducted in South Africa and Cameroon (30, 37). One study enrolled participants that booked for their ANC during first trimester and used only medical records to collect data (37). The second retrospective study enrolled participants admitted in the labour ward at term and used both study measures and medical records for data collection (30). Unlike prospective studies which recruited women over a period of 1 year (23, 29, 32, 36), retrospective studies selected women that booked over a narrow time period of 4 months (30, 37).

The 6 RCT studies were conducted across 4 SSA countries, with 5 of them enrolling women booking for their first ANC during first trimester (24, 31, 33-35). The remaining study enrolled participants who were in the third trimester (≥36 weeks) and those admitted at term in the labour ward (22). In contrast to observational studies that mostly had a single research site, the majority of RCT's recruited participants from multiple sites (22, 24, 34), with the HPTN 024 trial recruiting in multiple countries over a 2 year period (33). Only one RCT was primarily designed to investigate the association of maternal nutrition status and adverse birth outcomes where the intervention was vitamin supplementation to improve poor micronutrients in Tanzanian women (24). The other 5 studies were secondary data analysis for trials that originally investigated the effectiveness of different ART regimens as prevention of mother-to-child-transmission (PMTCT) strategies in Zambia and Uganda (22, 31, 35); and antibiotic interventions for improvement of birth outcomes in Tanzania, Zambia and Malawi (33, 34). By nature of the design, all RCT studies collected exposure and outcome data through study measures involving questionnaires, anthropometric measurements and laboratory testing of collected specimens performed by trained study personnel and/or clinicians during different study visits.

4.2 Sample Size

Most observational studies had sample sizes below 500 with 5 studies having a range between 91-437 (23, 29, 30, 32, 36) and the remaining study conducted in South Africa had 970 participants (37). Two RCTs conducted in Uganda had small sample sizes of 158 and 356 (31, 35); whereas 4 multicentre studies done in Tanzania, Zambia and Malawi had larger sample

sizes ranging from 1002-2149 participants (22, 24, 33, 34). In overall, the studies reviewed had sample sizes ranging from 91-2149.

4.3 Outcome Assessment

Eight studies reported preterm delivery as an outcome and 4 of them used the last menstrual period (LMP) to determine gestational age (24, 31, 33, 35). In addition to LMP, 2 of these 4 studies used an ultrasonography (US) gestation if LMP was discordant with US (31, 35). Ultrasonography is not routinely available in public maternity clinics in which most of these studies were conducted. As a result, only the APPLe trial conducted in Malawi strictly used US as a method of GA assessment because their primary outcome was accurate determination of factors associated with PTD, early PTD and late PTD (34). The remaining 2 studies do not report the PTD assessment method that they used (29, 37), one of them only mention having abstracted infant outcomes from medical records (37). Two studies determined term vs PTD using Ballard and Finnstrom scores (23, 33). These scoring methods are based on neurological and physical examination of new born maturity parameters immediately after birth (38).

Ten out of 12 studies reported birth weight as an outcome, with only 2 of them having study personnel who directly measured infant weight immediately after birth (23, 24). Four studies recorded birth weight from medical records (30, 31, 36, 37) and the other 4 did not report how they obtained data for this outcome (22, 29, 33, 35). In terms of size for gestational age, only 3 out of the 12 studies reported this outcome (23, 24, 35). Size for gestational age is measured by comparing the infant's GA, sex and their birth weight against standardised values to determine the percentile in which they fall in. The 3 studies used either LMP, US or Finnstrom score to determine the GA and direct measurement of infant weight by study clinicians (23, 24, 35), with one study not reporting how the birth weight was obtained (35).

4.4 Summary of Study Quality Appraisal

The aim of this study is to determine the association between high maternal BMI and GWG and adverse birth outcomes by HIV and ART status. Therefore, the quality of studies synthesised in this review was determined based on the design that clearly defined overweight/obese group, recruited participants in first trimester to allow measurement of gestational weight changes; adequate sample size to detect differences between comparison groups, and clearly defined outcomes of interest. None of the reviewed studies met all the criteria, however Gadama (37), Fouelifack et al. (30) and Anderson et al. (29) were the closest.

5. RESULTS FROM STUDIES REVIEWED

The results of the review of the included studies focuses on definitions and the association between exposures (high BMI and GWG) and adverse birth outcomes (PTD, LBW, HBW, SGA and LGA). The exposure/outcome definitions and key findings from the included studies are summarised in Tables 1b and 2, respectively.

5.1 Exposure Definitions and Comparison Groups

5.1.1 High Maternal BMI

High BMI in this review refers to overweight and obese group of participants. All 6 observational studies used standard, WHO-recommended BMI cut-offs of normal (18.5 - ≤24.9 kg/m^2), overweight (25.0 - ≤29.9 kg/m^2) and (obese ≥30.0 kg/m^2) categories for grouping participants. In contrast, most RCTs grouped participants based on BMI quartiles (22, 24) and tertiles (33, 35) as shown in table 1b. The reason for categorising BMI based on quartiles and tertiles is that weight measurements vary greatly by week of gestation regardless of trimester (22, 24) and the unavailability of standard BMI categories for pregnant women (33, 35). As a result of such grouping, the categories of interest which are overweight and obese groups were not explicitly indicated in these RCTs. None of the 12 studies justify the use of first trimester BMI measurement as an equivalent for pre-pregnancy BMI. Studies in other settings have justified the use of first trimester BMI, as weight change in early pregnancy is negligible (21, 39), while others use GA-adjusted BMI to approximate pre-pregnancy BMI (40, 41).

5.1.2 High GWG

Due to previous reports that have shown an association between GWG and adverse birth outcomes (42-44), 7 out of 12 studies investigated GWG as a risk factor for adverse birth outcomes in addition to baseline pregnancy BMI (24, 30-35). Two studies based weight gain on IOM weight gain recommendations, having sub-categories of inadequate, ideal and excessive weight gain without giving the numerical ranges (30, 32). The PROMOTE-Pregnant Women and Infants trial from Uganda had categories of low [<25th percentile (<0.1kg kg/wk)] vs high [≥25th percentile (≥0.1kg kg/wk)] weight gain (31, 35). Three studies had weight loss and weight gain categories (24, 33, 34); defined as weight loss (<0 kg/wk), low [0.01-0.18 (≤25 percentile)], normal [0.19-0.41 (>25 - ≤75 percentile)] and high [≥0.42 (>75 percentile)] weight gain (33). Most studies recruited women at their first trimester and therefore used overall weight

changes calculated as a difference between weight at enrolment and weight at 3rd trimester; only one study reported weight gain and/or loss per trimester (24).

5.1.3 HIV/ART Status

Four studies had asymptomatic, untreated women who were given nevirapine (NVP) regimen during labour (22, 24, 33, 34), 2 sub-studies from the PROMOTE-Pregnant Women and Infants trial used ART-naïve women on protease inhibitor vs non-nucleoside reverse transcriptase inhibitor-based ART regimen (35) and on lopinavir/ritonavir vs efavirenz plus lamivudine/zidovudine (31). One study used participants who were not on treatment and some who were on highly active ART (HAART) with no specific regimen names; whereas 5 studies do not report whether the HIV-infected women received any treatment or not (23, 29, 30, 32, 37).

5.2 Outcome Definitions

5.2.1 Preterm Delivery

A total of 8 studies examined PTD as an outcome. The WHO defines preterm delivery as delivery that occurs before completion of the 37 weeks of gestation; with sub-categories of extreme PTD (< 28 weeks), very PTD (28 - 32 weeks) and moderate to late PTD (32 - 37 weeks) (45). Seven studies used the WHO clinical definition of <37 weeks delivery gestation (23, 24, 29, 31, 33-35) with only one study not reporting the definition that they adopted (22). Some studies further sub-divided PTD into 2 categories of very PTD (<32 weeks) and PTD (<37 weeks) (31), while the APPLe trial had 3 sub-categories of early (24-33 weeks), late (34-36 weeks) and overall PTD (<37 weeks) (34).

5.2.2 Birth Weight

Ten studies reported birth weight as an outcome. The WHO categorises birth weight as low (<2500g), normal (2500-3999g) and large birth weight (≥4000g) (46, 47). Six studies defined LBW (23, 24, 29, 30, 33, 35) and macrosomia (30, 32, 37) using the standard WHO definitions, while 2 studies used continuous birth weight and reported mean birth weight (22, 36).

5.2.3 Size for Gestational Age

Size for gestational age is a measure of fetal growth based on gestation, sex and birth weight; and only 3 studies reported this outcome. There are no global standards for the categories of size for gestational age as this measure is based on specific population characteristics (48). Two

of them used the categories of SGA (<10th percentile), AGA (10 - 90th percentile) and LGA (>90th percentile) for the infant's gestational age based on USA standards (24, 35, 49). The third study reported IUGR and defined it as LBW with GA ≥ 37 weeks (23).

5.3 Association Between High Pregnancy BMI and Adverse Birth Outcomes in the Context of HIV Infection and/or ART Use

Many studies investigating the association of body weight and adverse birth outcomes in SSA focused on maternal malnutrition due to poverty and food insecurity affecting low income countries (50, 51). However, there has been a growing recognition of concurrent nutrition transition that has resulted in the rising epidemic of obesity. In Africa, obesity is reported to be >40% in women of reproductive age (52). Some studies report that the adverse birth outcomes associated with high BMI and GWG are HBW/macrosomia (≥4000g) and LGA infants (13, 53, 54). The proposed mechanism for the influence of maternal obesity on foetal growth is gestational diabetes mellitus characterised by insulin resistance which leads to increased maternal glucose and triglycerides (17, 55). Since maternal blood is passed to the foetus via the placenta, the foetus also experiences high levels of insulin, glucose and triglycerides which all promote foetal growth (55, 56). Macrosomic new-born infants are at risk of neonatal death mediated by complications of hypoglycaemia, respiratory distress and hyperbilirubinaemia (57). As a result, hypoglycaemic agents were proposed as a potential intervention that could be given to pregnant mothers at increased risk of diabetes (13), although the effectiveness and cost-benefit in SSA requires further investigation.

In contrast to macrosomia, other scholars report that high pregnancy BMI is associated with PTD, SGA and LBW and infants (14-16, 58, 59). The mechanism proposed for LBW and SGA in obese women is intrauterine foetal growth restriction mediated by reduced placental nutrient delivery due to reduced blood flow to the developing foetus (17). This materno-foetal hypo-perfusion is partly due to vasoconstriction caused by reduced affinity between vascular endothelial growth factor and it's receptor which inhibits the action of vasodilators (60, 61). In contrast, a study conducted in Cameroon did not observe any association between maternal BMI/GWG with LBW and macrosomia (30). However, the absence of association may have been due to the low prevalence of obesity (14% vs 49% normal weight) in the study population.

In terms of PTD, it is important to consider the type of PTD between medically indicated (MI) and spontaneous delivery in obese women. Medically indicated PTD is a deliberate medical

induction of labour or caesarean section to deliver the baby due to maternal or foetal complications. Spontaneous PTD is a natural premature rupturing of foetal membranes (PROM) resulting in preterm labour. There is vast evidence regarding the association of high BMI with MI-PTD, where pre-eclampsia is the main risk factor for early caesarean section in these women (19, 62, 63). However, there is controversy regarding the association of high BMI with spontaneous PTD. Some scholars found a protective potential of obesity against spontaneous PTD due to reduced levels of spontaneous uterine activity in obese women compared to normal or underweight women (64); whereas a more recent study found increased risk of spontaneous rather than MI-PTD in obese women (65). The differences in these findings could be attributed to the different population of women used. For example, Ehrenberg et al. (64) who found less spontaneous PTD used women who were already at high risk of PTD based on previous experience and hence likely to have had medical indications that led them to experience more MI than spontaneous PTD. On the other hand, Sung et al. (65) who found increased spontaneous PTD used women who had twin pregnancies rather than singletons. Twin pregnancies have 3-fold likelihood of PROM compared to singleton pregnancies (66) and this could have resulted in higher rate of spontaneous PTD that was observed in the study. The proposed mechanism for spontaneous PTD in obese women is the increased production of maternal inflammatory proteins such as interleukin-6 (IL-6), tumour necrosis factor-α (TNF-α) and IL-1β (17, 67). This inflammation is exacerbated by frequent genital and urinary tract infections in obese women, resulting in chorioamnionitis and increased risk of spontaneous PTD (19, 67).

Adding complexity to the association between high BMI and adverse birth outcomes is HIV infection which is prevalent in similar population group of women of child bearing age. This double burden poses a challenge in understanding the association between high BMI and adverse birth outcomes in the context of HIV, since HIV infection and/or ART-use in pregnancy have also been shown to be associated with adverse birth outcomes (26, 28, 68). Early studies conducted prior to availability of HIV treatment in low-income countries showed that HIV infection was associated with maternal wasting, PTD and LBW infants (23, 24, 69). The mechanisms for maternal wasting in HIV-infected women was multifactorial including inadequate diet, intestinal malabsorption, metabolic disturbances and increased production of cytokines due to onset of opportunistic infections (70). This suggest that PTD during this period may have been due to opportunistic infections in the advanced HIV infection stage which consequently led to disturbance of immune system and premature labour. Whereas LBW infants

could have been due to insufficient nutrients delivered to the baby, resulting in foetal growth restriction.

In the reviewed studies, 3 RCTs conducted between 1992-2003 in Tanzania, Zambia and Malawi which investigated birth outcomes of HIV-infected, untreated women had similar findings of greater risk of PTD, LBW and SGA linked to HIV infection-related weight loss and low BMI (22, 24, 33). The same conclusions are echoed in the APPLe trial conducted in Malawi which showed that low pre-pregnancy BMI and inadequate weight gain in pregnancy is associated with PTD while high BMI and weight gain improved these outcomes (34). As a result, some of these studies report increased maternal BMI as protective against these adverse birth outcomes (22, 24). In agreement, a micronutrient supplementation trial conducted in Tanzania showed that improved weight gain due to supplementation of vitamin B, C and E in HIV-infected women reduces PTD and LBW by almost 40% (71). However, these studies reporting high BMI to be protective did not indicate the upper end limit of the protective weight. The reviewed multi-country HPTN 024 trial showed that both weight extremes of low and high maternal weight are associated with PTD in HIV-infected women [36].

When ART became available, it had evident benefits of improved maternal health and reduced mother-to-child transmission of HIV infection. However, despite this advancement, a certain group of women still struggle to gain adequate weight during pregnancy, resulting in persistent adverse birth outcomes. For example, the PROMOTE-Pregnant Women and Infants trial in Uganda which randomised women to receive lopinavir/ritonavir versus efavirenz plus lamivudine/zidovudine found increased risk of PTD and LBW infants in women with inadequate weight gain during pregnancy; while women with high BMI at enrolment had 30% reduction in LBW infants (31, 35). However, the upper limit of the weight that was beneficial in the reduction of LBW was not indicated, as the highest category of BMI in this study was $\geq$23 kg/m^2.

Two of the reviewed studies conducted in South Africa included clear sub-categories of high BMI (overweight, obese and morbidly obese) vs normal BMI, they found a maternal BMI-dependent increase in the risk of PTD and macrosomic infants (32, 37). Although these 2 studies had HIV-infected groups, they did not report results according to HIV or ART status. A more recent finding that reported adverse birth outcomes by HIV status, found an increased risk of PTD and LBW in HIV-infected women, with women who are both HIV-infected and obese having higher risk of LBW compared to HIV-uninfected obese women (29). Low birth weight

infants in these women is thought to be due to obesity-related inflammation and oxidative stress exacerbated by HIV co-infection, resulting in endothelial dysfunction and compromised blood flow to the foetus (29, 72).

Independent from HIV infection, ART has a detrimental impact on metabolic dysregulation which can greatly influence fetal growth. Regimens such as nucleoside reverse transcriptase inhibitors (NRTI's) and protease inhibitors (PI's) can sometimes increase the risk of lipodystrophy which is fat redistribution in the abdominal areas (73). In turn, lipodystrophy can further increase the risk of development of cardiovascular disease including diabetes mellitus, hyperlipaemia and pre-eclampsia (74). Consequently, these pregnancy complications have been implicated in mediating PTD, HBW and LGA infants. These adverse birth outcomes have long-term effect on offspring's health including neurodevelopmental delays and exposure to early childhood obesity and related morbidities (75). Since growing evidence suggests increased obesity prevalence in HIV-infected women that are using ART, incorporation of obesity prevention programs into routine HIV care is recommended to minimise adverse birth outcomes (29, 37, 76-78).

5.4 Methodological Differences in the Literature

The studies reviewed present different conclusions regarding the association between high BMI and adverse birth by HIV and ART status. These differences could be attributed to the different study populations, study designs and exposure groups as outlined below.

5.4.1 Study Population

The studies reviewed were conducted across 6 countries in SSA. These countries have different diets, HIV infection prevalence and background adverse birth outcomes due to other risks factors. Depending on the region in which the participants were recruited, women could have lower or higher prevalence of pre-pregnancy obesity. For example, in Rwanda it has been shown that obesity prevalence in women is higher in urban areas than in rural areas (79) which is common for any other country. Therefore, the findings of the study would be influenced by the proportion of obese women in the study which depends on the setting in which it was conducted as some studies recruited in rural and others in urban hospitals (24, 31). Besides in-country differences, obesity prevalence ranges from a high of 68.5% in South African women to a low of 20% in Zambia (10). Therefore, it is plausible that Chaambwa (36) did not find any difference in obesity prevalence between HIV-infected and -uninfected women in Zambia

whereas Anderson et al. (29) found a higher prevalence of obesity in HIV-infected women in South Africa. Indeed, this result could also be attributed to the difference in HIV infection prevalence in these 2 countries.

The timing of the study also affects the type of HIV-infected individuals that were included in the different studies. Studies that were conducted prior to 2002 used women who were not on treatment and hence could have been sicker and lost weight which influenced the adverse birth outcomes (23). Although the majority of studies conducted prior to 2010 also had untreated women, they may have been healthier with CD4 count >350 and were only given NVP regimen during delivery; as such, their outcomes would differ from those that had to be placed on HAART (22, 33, 36). Women on HAART have been shown to be at higher risk of adverse pregnancy outcome due to production of high levels of IL-10 rather than IL-2, favouring cytotoxic uterine environment and preterm labour (80).

Other SSA countries are faced with anaemia and malaria as risks factors for adverse birth outcomes hence they included these factors in their investigations in addition to high BMI and HIV (33-35). Therefore, their findings would be different from those studies that do not have a concerning prevalence of these conditions in pregnant women. The studies also had participants with varying maternal ages of <20 – >40 years (33, 36). Old age increases the likelihood of multiparity and pregnancy complications which increases the risk of adverse birth outcomes (81) and this could attribute to differences observed in the studies reviewed.

5.4.2 Study Designs and Exposure Groups

Half of the studies reviewed were observational cohorts. In such studies there is a risk of misclassification due to measurement error of the exposure, which could lead to under or over estimation of the outcome. In addition, the exposed group tends to have other underlying risks factors for the outcome as risks factors cluster together. For example, Castetbon et al. (23) found that the HIV-infected participants had lower level of education compared to the uninfected group. This difference in demographics could be important in providing overestimated conclusions regarding adverse birth outcomes. Hence, if there is an imbalance in the distribution of risks factors among the comparison groups, the findings are normally unreliable. The 2 retrospective cohorts on the other hand had a limitation of missing information that could have a significant impact on the findings (30, 37). Gadama (37) excluded about 380 women in the

analysis and was left with a sample size of 970 due to missing medical records and missing variables in some of the records that were found.

In contrast, half of the studies reviewed were RCTs which have intense data collection that minimises missing information during the analysis. RCTs are characterised by randomisation of participants to 2 or more comparison groups. This randomisation reduces biased conclusions because it allows random distribution of known and unknown risks factors such that, if maintained, the differences that arise can be attributed to the intervention being studied. Hence, this type of design is regarded as being the best in providing reliable scientific evidence, provided they are planned, conducted, analysed, and reported appropriately as per research question (82). Unfortunately, in this case, all these trials were not primarily designed to study the exposure of interest hence their data may also be questionable. As a result, the obese groups were not clearly defined hence their findings are biased towards lower ends of maternal weight and adverse birth outcomes (31, 33-35). This led to a recommendation for interventions to improve maternal weight in these RCTs (33). However, there could have been a discrepancy regarding the association of maternal weight and adverse birth outcomes in these studies as they did not have an indication of overweight/obese groups in their population as their highest BMI category was >24.00 kg/m^2 with no clear upper-end limit (23, 24, 31, 33-35). In contrast, most observational studies had standard weight categories (overweight, obese vs normal weight) and they found increased maternal weight to be associated with adverse infant outcomes and recommended weight reduction interventions in pregnant women (29, 36, 37).

6. SUMMARY

The studies reviewed show that available data do not reflect the trend of knowledge advancement regarding the relation of obesity and HIV infection. Most studies that investigated the association of BMI and adverse birth outcomes in HIV-infected populations were conducted in the era where HIV treatment was unavailable or only available during delivery. Therefore, they investigated maternal weight in the context of HIV-related weight loss rather than obesity; and hence concluded that low BMI is associated with adverse birth outcomes (23, 24, 31, 33-35). Recent studies that included obese women in their study population report that high BMI is associated with adverse pregnancy outcomes (30, 32, 36, 37). However, these studies did not focus on HIV infection and ART-use in pregnancy despite the growing evidence of high obesity prevalence in these women (77, 78). Instead, they included HIV status due to the awareness that some study participants may have the infection, a known confounder for adverse birth

outcomes. The only study that was primarily designed to investigate both high BMI and HIV infection as risks factors for adverse birth outcomes was Anderson et al. (29). However, this study recruited women from a heavily polluted area because their intention was also to study ambient air pollution which has been reported to be a risk factor for adverse birth outcomes (83). Therefore, there is limited data regarding the association of high BMI and adverse birth outcomes by HIV and ART status in SSA.

7. RECOMMENDATIONS

Although there is a clear shift in the relation of HIV infection and maternal weight from weight loss to weight gain, research has not focused on studying these risks factors together. It is known that HIV infection is independently associated with maternal weight loss which in turn is related to adverse birth outcomes such as PTD, SGA and LBW. On the other hand, obesity has also been independently shown to be associated with both similar and opposite (macrosomia and LGA) adverse birth outcomes as HIV infection. Preterm delivery, SGA and LBW are associated with adverse health consequences including increased neonatal and infant mortality (84). Low-income countries are particularly vulnerable to this problem as they lack resources for basic care for infections and breathing difficulties for these babies (45). Even in areas that have advanced medical care, infants that overcome poor birth outcomes face significant cognitive, behavioural, and developmental challenges in their childhood and throughout their lifetime (45, 84, 85). Due to the evident benefit of HIV treatment on maternal and child health, there has been a dramatic increase in ART-use in HIV-infected pregnant women due to the WHO guidelines of UTT (86, 87). Consequently, recent data suggests that overweight and obesity prevalence is high in HIV-infected women using ART (77-79, 88-91). Therefore, research needs to establish whether the combined association between both obesity and HIV/ART-use in pregnancy and adverse birth outcomes exists.

Table 1a. Summary and key features of quality of included studies

Study	Year published	Country	Time-period	Setting	Study population	Sample size	Study design	Data collection
Castetbon	1999	Rwanda	1992-1993	Public hospital	Pregnant women with GA ≤28 weeks	371	Prospective cohort	Study measures
Villamor	2004	Tanzania	1995-1997	4 Maternity clinics	Pregnant women with GA=12-27 weeks	1002	RCT	Study measures
Kruger	2005	South Africa	1 year (not mentioned)	Maternity clinic	Pregnant women booking for 1st ANC visit, with GA<28 weeks and singleton pregnancy	91	Prospective cohort	Study measures
Banda	2007	Zambia	2000-2001	2 Maternity clinics	Pregnant women with GA ≥36 weeks OR at arrival in labour ward	1211	RCT	Study measures
Mehta	2008	Tanzania, Zambia and Malawi	2001-2003	4 clinics; 1 in Zambia, 1 in Tanzania and 2 in Malawi,	Pregnant women with GA = 20-24 weeks	2126	RCT	Study measures
Young	2012	Uganda	2009-2011	Public hospital	Pregnant women with GA = 12-28 weeks	158	RCT	Study measures
Gadama	2013	South Africa	Jan - Apr 2011	2 Maternity clinics	Pregnant women booking for 1st ANC visit between Jan-Apr 2011	970	Retrospective cohort	Data abstraction
Koss	2014	Uganda	2009-2012	Public rural hospital	Pregnant women booking for 1st ANC visit who are ART-naïve with GA 12-28 weeks	356	RCT	Study measures
van den Broek	2014	Malawi	n/a	3 Rural and 1 peri-urban health centres	Pregnant women with GA <24 weeks	2149	RCT	Study measures
Fouelifack	2015	Cameroon	Jan - Apr 2014	Teaching hospital	Women with singleton, term delivery between Jan - Apr 2014	462	Retrospective cohort	Study measures Data abstraction
Chaambwa	2016	Zambia	2015-2016	Teaching Hospital	Pregnant women at term admitted in labour ward	262	Prospective cohort	Study measures Data abstraction
Anderson	2018	South Africa	2013-2014	4 Maternity clinics	Pregnant women in their 1st trimester	437	Prospective cohort	Study measures

Table 1b. Summary and key features of quality of included studies (exposures and outcomes)

Study	**Exposures (definition)**		**Comparison groups**	**Outcomes (definition)**			**Outcomes assessment**
	BMI (kg/m^2)	**GWG**	**HIV/ART**	**Preterm birth**	**Birth weight**	**Size for GA**	
Castetbon	Normal (25) vs high (>25)	n/a	HIV+ (Asymptomatic, elevated CD4 count, no treatment information) vs HIV-	<37 weeks	LBW: <2500g	IUGR: LBW with GA ≥37 weeks	• Finnstrom score • Clinical examination (by study clinicians)
Villamor	Grouped by week of GA and categorised to quartiles 1-4	• Regression slope ≤0 'Weight loss'; slope <25 'Low rate of weight gain' <u>3 Types</u> • Overall: Enrolment and Delivery • T2: GA week 12 and 26 • T3: GA 27 and delivery	HIV+ (untreated, 24% >stage 1; 12% cd4<200/mm3)	<37 weeks	LBW: <2500g	SGA: <10th percentile	• LMP • Clinical examination (by study midwife)
Kruger	• Underweight: <19.8 • Normal: 19.8 - ≤26.0 • Overweight: >26.0 - <29.0 • Obese: ≥29.0"	• Inadequate: < IOM recommend • Ideal: = IOM recommendation • Excessive: > IOM recommend	HIV+ vs HIV-	n/a	Macrosomia: > 4000g	n/a	• US • Obstetric records
Banda	<u>Quartiles</u> • Q1: ≤22.7 • Q2: >22.7 - ≤24.5 • Q3: >24.5 - ≤26.8 • Q4: >26.8	n/a	HIV+ (NVP regimen) vs HIV-	n/a	Mean birth weight	n/a	NR
Mehta	<u>Tertiles</u> • T1: <21.8 • T2: 21.8 – 23.9 • T3: ≥24.0	• Weight Loss: <0 kg/wk • Low: 0.01-0.18 (≤25 percentile) • Normal: 0.19-0.41 (>25 - ≤75 percentile) • High: ≥0.42 (>75 percentile)	HIV+ (NVP at labour)	<37 weeks	LBW: <2500g		• SFH • Ballard Examination • LMP
Young	<u>Tertiles</u> • T1: <20.43 • T2: 20.43-22.59 • T3: >22.59	<25th percentile (<0.1kg per week) vs ≥25th percentile (≥0.1kg per week)	WHO stage1; ART-naïve (protease inhibitor or non-nucleoside reverse transcriptase inhibitor-based ART regimen)	<37 weeks	LBW: <2500g	SGA: <10th percentile	• LMP • US

Study	Exposures (definition)			Outcomes (definition)			Outcomes assessment
	BMI (kg/m^2)	**GWG**	**HIV/ART**	**Preterm delivery**	**Birth weight**	**Size for GA**	
Gadama	• Normal: 18.5 - 24.9 • Overweight: 25.0 - 29.9 • Obese: 30.0-39.9 • Morbidly Obese: ≥40.0	n/a	HIV+ and HIV-	n/d	• Macrosomia: ≥ 4000g	n/a	Obstetric records
Koss	• <20 • 20 <23 • ≥23	• <0.1 kg/week • ≥0.1 kg/week	ART-naïve: lopinavir/ritonavir versus efavirenz PLUS lamivudine/zidovudine in both arms	• Very preterm: <32 weeks • Preterm: <37 weeks	n/a	n/a	• LMP if concordant with US GA • US if LMP and US discordant
van den Broek	• Underweight: <18.5 • Normal: > 18.5	• Weight gain: n/d • Weight loss: n/d	HIV+ (untreated, only given at delivery) and HIV-	• Overall: <37 weeks • Early: 24-33 weeks • Late: 34-36 weeks	n/a	n/a	US
Fouelifack	• Underweight: <18.5 • Normal: 18.5 - ≤24.9 • Overweight: 25.0 - ≤29.9 • Obese: ≥30.0	• < IOM recommendation • = IOM recommendation • > IOM recommendation	HIV+ and HIV-	n/a	• LBW: <2500g • Macrosomia: ≥ 4000g	n/a	Obstetric records
Chaambwa	• Normal: 18.5-25.0 • Obese: >30	n/a	HIV+ (5.3% not on treatment; 17.6% on HAART) vs HIV-	n/a	Mean birth weight	n/a	Obstetric records
Anderson	• Non-obese: <30 • Obese: > 30	n/a	HIV+ vs HIV-	• Term: >37 weeks • Pre-term: <37 weeks	• NBW: >2500g • LBW: <2500g	n/a	NR

*n/a – not assessed
*n/d – not defined
*NR – not recorded

Table 2. Key findings from included studies

Study	Key Finding
Castetbon	• Mean weight lower for HIV+ at enrolment (59.4kg vs 62.2kg); and at last ANC visit (61.3kg vs 64.1kg); due to infection not SES • LBW higher in HIV+ (18.6% vs 9.3%) • Low maternal weight at last visit associated with LBW (OR 0.94, 95% CI 0.89-0.99) • LBW mechanism: HIV infection → intestinal malabsorption and metabolic disturbance → reduced maternal weight →reduce nutrient to foetus →LBW infant • Preterm births higher in HIV+ (21.5% vs 11.9%) • IUGR higher in HIV+ (6.8% vs 2.6%)
Villamor	• Prevalence of pregnancy loss = 8%, preterm birth = 25%, LBW =11% and SGA = 11% • Baseline Q4 weight (231g, 95% CI 132-330) and Q4 BMI (180g, 95% CI 90-271) associated with increased birth weight • Baseline Q4 weight (RR 0.47, 95% CI 0.24-0.94) and Q4 BMI (RR 0.40, 95% CI 0.23-0.70) associated with reduced risk of SGA • Weight loss (RR 1.85, 95% CI 1.40-2.44) and low weight gain (RR 1.34, 95% CI 1.34) associated with preterm delivery
Kruger	• Women with higher pre-pregnancy BMI gained excessive weight during pregnancy • Overweight/obese women had more macrosomic babies (9.7% vs 1.6% normal weight)
Banda	• Unit increase in BMI increases infant birth weight to a lesser extent (but not significant) in HIV-infected women (28.3g, 95% CI 14.0-42.6) vs HIV uninfected (32.7g, 95% CI 23.5-41.9)
Mehta	• T1 BMI (vs T3) is associated with preterm births (OR 1.82, 95% CI 1.34-2.46) and LBW (OR 2.09, 95% CI 1.41-3.08) • Weight loss (vs normal weight) is associated with preterm births (OR 2.16, 95% CI 1.55-3.00) • High weight gain (vs normal weight) is associated with preterm births (OR 1.55, 95% CI 1.14-2.12) • Weight loss (vs normal weight) is associated with LBW (OR 2.30, 95% CI 1.52-3.47)
Young	• Prevalence of LBW =19.6%, preterm delivery = 17.7% and SGA =15.5% • Increased maternal weight associated with 30% reduced risk of LBW (OR 0.70, 95% CI 0.52-0.95) • Low weight gain associated with LBW (OR 6.18, 95% CI 1.80-21.1) • Low weight gain associated with preterm birth (OR 3.46, 95% CI 1.18-10.15)
Gadama	• In HIV-infected group, there were more women in the obese category than normal weight • Risk of having macrosomic babies increased with increasing maternal BMI; overweight (OR 1.69, 95% CI 0.76-3.77), obese (OR 4.71, 95% CI 2.45-9.06), morbidly obese (OR 9.2, 95% CI 4.61-18.55) compared to normal weight • Risk of preterm deliveries increased with increasing maternal BMI; obese (OR 1.10, 95% CI 0.68-1.95), morbidly obese (OR 2.26, 95% CI 1.20-4.15)

Study	Key Finding
Koss	• There was no difference in risk of preterm and very preterm births between the 2 ART arms (OR = 1.12, 95% CI 0.63–2.00) • Women who gained less than 0.1 kg/week versus 0.1 kg or more per week had higher odds of preterm birth (OR = 2.49, 95% CI 1.38–4.47)
van den Broek	• Greater proportion of women with preterm births (vs term) had underweight BMI (9.3% vs 3.2%) • Women with preterm births (vs term) gained less weight between 1st and 3rd trimester (2.94 vs 3.39) • Increasing BMI (OR = 0.91, 95% CI 0.85-0.97) and weight gain (OR = 0.89, 95% CI 0.82-0.97) are associated with reduced odds of preterm births
Fouelifack	• Prevalence of LBW =11% and macrosomia= 7% • No significant association between BMI/GWG with LBW and macrosomia
Chaambwa	• There were no differences in BMI between HIV+ and HIV- mothers • Obesity is associated with increased birth weight (OR 3.60, 95% CI 2.05-6.32) than normal weight women
Anderson	• High prevalence of obesity in HIV+ women (45.3% vs 27.4% non-obese) • HIV+ women had higher risk of having LBW infant (14.67% vs 10.09% HIV-) • HIV+ women had higher risk of having preterm birth (18.67% vs 8.26% HIV-) • Being obese and HIV+ increased risk of having a LBW (28.99% vs 5.38% non-obese) • LBW mechanism: compromised blood flow to the foetus due to inflammation, oxidative stress, endothelial dysfunction and atherosclerosis caused by obesity and HIV infection

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PART C: MANUSCRIPT

Association Between High Body Mass Index and Adverse Birth Outcomes by HIV and ART Status in Cape Town, South Africa: A Prospective Cohort Study

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[1] The target peer reviewed journal that was chosen to guide the formatting of this manuscript is the British Medical Journal (**BMJ) Open.** The requirements set out in the instructions for authors are included as appendix 5A in the appendices section. As per MPH guidelines, the co-authors are not listed in the main manuscript, but their contributions are recognised in the acknowledgements section of this dissertation. As well, the figures and tables are inserted in the text and not appended at the end of the manuscript.

ABSTRACT

Objectives: To examine the association of high BMI (overweight and obese) and gestational weight gain (GWG) with adverse birth outcomes by HIV and ART status in women seeking antenatal care.

Design: Observational prospective cohort study.

Setting: Recruitment took place in a maternity obstetric unit (MOU) at a primary healthcare facility located in a peri-urban area in Cape Town.

Participants: A total of 3254 HIV-infected and HIV-uninfected black women seeking antenatal care at Gugulethu MOU was enrolled. A subset of 549 HIV-infected women who booked early (≤24weeks) was prospectively followed through delivery.

Primary and Secondary Outcome Measures: The adverse birth outcomes of interest were preterm delivery (PTD), low/high birthweight (LBW/HBW) and small/large gestational age (SGA/LGA) infants.

Results: There was no association (aOR 1.06, 95% CI 0.75-1.49) between obese BMI and PTD, regardless of HIV and ART status compared to normal BMI. However, obese BMI was negatively associated with LBW (aOR 0.53, 95% CI 0.39-0.72) and SGA (aOR 0.55, 95% CI 0.41-0.75) compared to normal BMI. Inversely, obese BMI was positively associated with HBW (aOR 2.00, 95% CI 1.13-3.57) and LGA (aOR 1.98, 95% CI 1.40-2.80) regardless of HIV and ART status compared to normal BMI. Restricting the analysis to obese HIV-infected women only, revealed a counter effect of the two conditions where the frequencies of both LGA and SGA are high. Although the association of high GWG and adverse birth outcomes showed similar trends as obese BMI, statistical significance was not consistently obtained.

Conclusions: Obese HIV-infected women appear to be cushioned by their BMI against LBW and SGA when compared to normal BMI. However, comparison of these outcomes amongst women who are either obese or HIV-infected reveal a higher burden of both SGA and LGA infants in obese HIV-infected women, regardless of ART initiation status.

Strengths and Limitations of this Study

- Large sample size, enabled detection of differences between groups.
- Comparison of adverse birth outcomes in multiple groups of women: obese only, HIV-infected only and obese HIV-infected women who initiated ART before and during pregnancy.
- Use of IOM guidelines for GWG may not be applicable to African Black women.
- Small sample size for the subset of women studied for GWG.

1. INTRODUCTION

Obesity has previously been regarded as the disease of the rich that is highly prevalent in Western countries. However, recent evidence shows a constant rise in obesity in low-income countries (1, 2). South Africa is the most obese region in Sub-Sahara, with women of child-bearing age carrying the most burden of approximately 70% (3, 4). Consequently, the South African Department of Health recently declared obesity driven non-communicable diseases (NCD) as being amongst the top 10 leading causes of mortality and morbidity (3). Overweight and obese women are likely to gain more weight during pregnancy and to retain the weight after delivery (5). Therefore, women from SSA countries are at high risk of accumulating weight due to frequent and short-term interval pregnancies; in addition to excess consumption of high fat/sugar diets.

Foetal development is dependent on maternal nutrition status which ultimately determines obstetric and neonatal outcomes (6). Consequently, infants born from women with pre-pregnancy obesity or excessive gestational weight gain have increased risk of adverse health outcomes. The adverse birth outcomes related to high BMI (overweight and obese) include macrosomic (birth weight ≥4kg) and LGA (>90th percentile) infants (7, 8). This is supported by longitudinal data showing an increase in mean infant birth weight paralleled by increased mean maternal weight at first antenatal care booking (9-11).

Big babies are at greater risk of congenital anomalies, low Apgar score, asphyxia and perinatal or neonatal death (12, 13). Those that survive these poor outcomes are likely to experience childhood obesity and the associated cardiovascular and metabolic complications which lead to premature mortality (14-17). In contrast, other studies report that high BMI is associated with LBW (<2500g), SGA (<10th percentile) and PTD (<37 weeks) (18-22). Preterm and LBW are amongst the leading causes of neonatal and under-5 years child mortality (23). Low-income countries are particularly vulnerable to these adverse outcomes as they lack resources for basic care for infections and breathing difficulties for these babies (24, 25). On the other hand, infants that do overcome these poor birth outcomes face significant cognitive, behavioural and developmental challenges in their childhood and throughout their lifetime (23, 24, 26).

Adding complexity to the association between high BMI and adverse birth outcomes is HIV infection which mostly affects the same population group of women of child-bearing age. Despite the ART program being one of the greatest successes in public health interventions, strong evidence from HIV prevalent countries suggests that HIV infection and/or ART-use in

pregnancy are associated with LBW, SGA and PTD (27-31). The established independent association of obesity and HIV/ART with adverse birth outcomes is due to vast research which has focused on studying these exposures separately. As a result, there is limited literature on the combined impact between the double burden of obesity and HIV and adverse birth outcomes. Therefore, we examined the association between high pregnancy BMI and adverse birth outcomes by HIV and ART status in women seeking ANC in Cape Town, South Africa.

2. METHODS

2.1 Study Design

This study was a secondary data analysis of a large observational cohort that investigated Prematurity Immunology in Mothers and their Infants (PIMS study).

2.2 Study Setting

Study participants were recruited at Gugulethu MOU. Gugulethu is a semi-urban area with a population of 98 468, predominantly made up of 98.8% black African ethnic group with low socioeconomic status (32, 33). The MOU provides antenatal, obstetric and infant care for approximately 5 000 women (per annum) with low risk pregnancies, who deliver with the help of midwives. Women with previous history of pregnancy complications and first ANC bookers who are considered as high-risk pregnancies are referred to secondary and tertiary health care facilities.

2.3 Inclusion and Exclusion Criteria

This analysis included HIV-uninfected and HIV-infected women aged ≥18 years, with singleton pregnancy, booking for their first ANC between April 2015 and October 2016 in Gugulethu MOU. Pregnant women with multiple pregnancies, underweight BMI (<18.5) and gestational weight loss were excluded from the analysis since these are potential confounders of adverse birth outcomes (Figure 1). Specifically, the population of interest for this study are women who have normal, overweight and obese BMI and women who gained weight during pregnancy. Women with missing weight/height measurements and total gestational weight gain were also excluded.

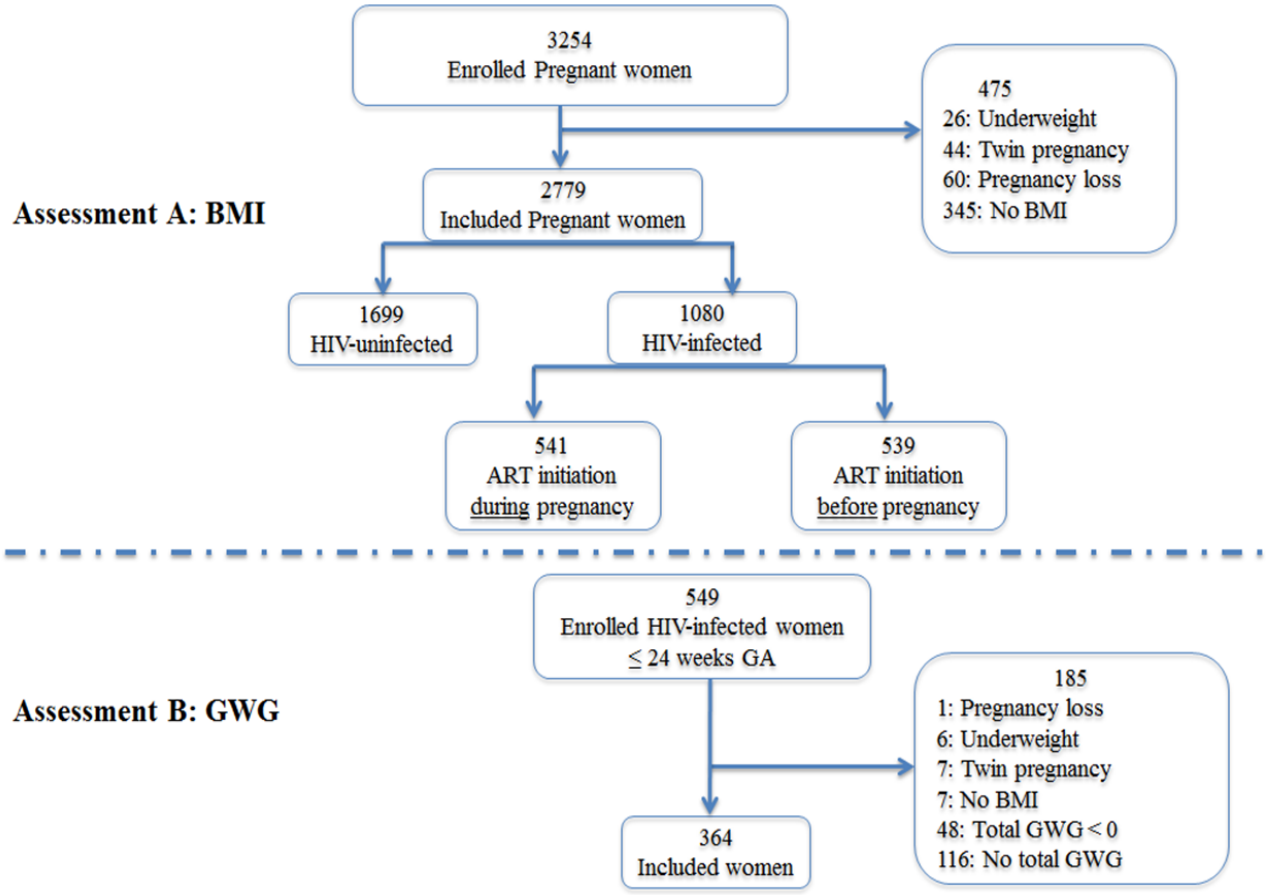

Figure 1. Flow diagram showing the selection of women included in the analysis

2.4 Study Procedures and Data Collection

The parent study was reviewed and approved by the University of Cape Town Faculty of Health Sciences Research Ethics Committee (UCT-HREC) (739/2014) (Appendix 2B) and the University of Southampton Institutional Review Board (12542 PIMS) (Appendix 2C). Written informed consent for data collection using study questionnaires and abstraction of medical record data was obtained from all participants (Appendix 3A and 3B). Ethical approval for the current study was obtained from the UCT-HREC (350/2018) (Appendix 2A) and no further informed consent was required from the study participants.

Exposure measurements: weight and height measurements for BMI calculation were performed by health practitioners as part of routine ANC and abstracted into the study abstraction form (Appendix 4B). BMI was categorised into normal (18.5-24.9), overweight (25-29.9) and obese (≥30) in kg/m^2 categories by HIV and ART status (Assessment A). Gestational weight gain assessment was only performed in the subset of HIV-infected women that booked early (≤24

weeks) as they had follow-up study visits and weight measurements collected by trained study personnel (Assessment B). Total weight gain was calculated as the difference between weight at last study visit before delivery and first ANC visit; and was categorised as low, adequate and high weight gain in relation to the IOM guidelines (34, 35).

Outcome assessment: gestational age at booking is routinely measured by health practitioners using last menstrual period and symphysis-fundal height (SFH). As part of study procedures, some participants had their GA assessed by ultrasonography operated by an experienced sonographer. This booking GA and date of delivery obtained from clinic records were used to calculate gestation at delivery. Delivery GA was categorised into term (≤37) and preterm (<37) deliveries in weeks. Infant birth weight and sex were obtained from data abstracted from medical records. Infant birth weight was categorised into low (<2500), normal (2500 – 3999) and high (≥4000) birthweight in g. Size for gestational age was obtained based on infant gestational age, birthweight and sex using INTERGROWTH-21st Project tool; and was categorised into small (<10th), appropriate (10-90th) and large (>90th) gestational age in percentiles (36).

Additional information regarding demographics, medical history and obstetric was obtained from medical records and from questionnaires completed at various study follow-up visits for the subset of HIV-infected women that was followed through to 12 months post-partum.

2.5 Data Analysis

All data was analysed using STATA (version 14.0, Stata Corporation, College Station, TX, USA). Numerical continuous variables are presented as mean (SD) and/or medians (IQR). Categorical variables are presented as counts and proportions, Chi-Squared test was used for comparison between groups. The analysis focused on the exposures:

i) BMI only (normal, overweight and obese)
ii) BMI and HIV status (HIV-uninfected vs HIV-infected)
iii) BMI and ART status (ART initiation before pregnancy and ART initiation during pregnancy) and;
iv) GWG (low, adequate and high)

The association between exposures and birth outcomes (PTD, LBW, HBW, SGA and LGA) was tested using logistic regression; and results are presented as adjusted odds ratios (aOR) with 95% confidence intervals (CI). All models were adjusted for *a priori* confounders such as

maternal age, gestation at enrolment, parity and previous PTD (37). Differences between groups were considered statistically significant at $p<0.05$.

3. RESULTS

3.1 Assessment A

A total of 2779 women with live singleton births were included in this analysis: 556 normal BMI (20%), 807 overweight (29%) and 1416 obese (51%). In total, 1699 were HIV-uninfected (61%) and 1080 HIV-infected (39%), of which 539 (50%) initiated ART before pregnancy and 541 (50%) during pregnancy (Figure 1). Obese BMI prevalence was similar between HIV-uninfected (51%) and -infected women (50%). Obese HIV-infected women were more likely to be older, book early for ANC, have higher gravid and parity compared to obese HIV-uninfected women (Table 1).

Table 1. Maternal baseline characteristics of enrolled participants with live singleton births by BMI and HIV status (n = 2779).

	Total n = 2779	HIV-uninfected n = 1699				HIV-infected n = 1080			
		BMI				BMI			
		Normal n = 336	Overweight n = 492	Obese n = 871	Chi^2 p-value	Normal n = 220	Overweight n = 315	Obese n = 545	Chi^2 p-value
Age (years)					<0.001*				<0.001*
<20	273 (10)	86 (26)	81 (16)	53 (6)		16 (7)	18 (6)	19 (3)	
20-24	604 (22)	112 (33)	150 (30)	187 (21)		46 (21)	46 (15)	63 (12)	
25-29	786 (28)	81 (24)	143 (29)	258 (30)		69 (31)	84 (27)	151 (28)	
30-34	700 (25)	44 (13)	86 (17)	213 (24)		69 (31)	105 (33)	183 (34)	
≥35	416 (15)	13 (4)	32 (7)	160 (18)		20 (9)	62 (20)	129 (24)	
Median (IQR)	28 (23-32)	23 (20-27)	25 (22-29)	28 (24-33)		28 (24-32)	30 (25-34)	31 (26-34)	
Height (cm)					0.517				0.490
≤155	939 (34)	103 (31)	160 (33)	290 (33)		74 (34)	103 (33)	209 (38)	
156-161	1053 (38)	138 (41)	182 (37)	349 (40)		79 (36)	118 (37)	187 (34)	
≥162	787 (28)	95 (28)	150 (30)	232 (27)		67 (30)	94 (30)	149 (27)	
Median (IQR)	158 (154-162)	158 (155-162)	158 (154-162)	158 (154-162)		159 (154-163)	158 (154-163)	157 (154-162)	
Obstetrics									
GA (weeks)					0.006*				0.195
1st trimester (≤13)	712 (26)	84 (25)	100 (20)	197 (23)		72 (33)	87 (28)	172 (32)	
2nd trimester (14-28)	1598 (58)	212 (63)	298 (61)	510 (59)		118 (54)	171 (54)	289 (53)	
3rd trimester (>28)	406 (15)	32 (10)	78 (16)	152 (17)		21 (10)	51 (16)	72 (13)	
Median (IQR)	19 (13-25)	18 (13-23)	20 (14-27)	20 (14-26)		17 (12-21)	19 (13-26)	18 (12-24)	
Missing	63 (2)	8 (2)	16 (3)	12 (1)		9 (4)	6 (2)	12 (2)	
Gravidity					<0.001*				<0.001*
1	673 (24)	151 (45)	164 (33)	177 (20)		51 (23)	62 (20)	68 (12)	
2	951 (34)	108 (32)	179 (36)	289 (33)		89 (40)	102 (32)	184 (34)	
≥3	1148 (41)	77 (23)	149 (30)	404 (46)		78 (35)	149 (47)	291 (53)	
Median (IQR)	2 (2-3)	2 (1-2)	2 (1-3)	2 (2-3)		2 (2-3)	2 (2-3)	3 (2-3)	
Missing	7 (0.3)	0	0	1 (0.1)		2 (1)	2 (0.6)	2 (0.4)	
Parity					<0.001*				<0.001*
0	822 (30)	183 (54)	192 (39)	205 (24)		69 (31)	82 (26)	91 (17)	
1	1038 (37)	100 (30)	185 (38)	326 (37)		94 (43)	106 (34)	227 (42)	
≥2	911 (33)	53 (16)	115 (23)	339 (39)		55 (25)	125 (40)	224 (41)	
Median (IQR)	1 (0-2)	0 (0-1)	1 (0-1)	1 (1-2)		1 (0-2)	1 (0-2)	1 (1-2)	
Missing	8 (0.3)	0	0	1 (0.1)		2 (1)	2 (0.6)	3 (0.5)	
Prior preterm#					<0.001*				0.017*
Yes	200 (7)	15 (4)	27 (5)	64 (7)		21 (10)	30 (10)	43 (8)	
Prior pregnancy loss#					<0.001*				0.115
Yes	333 (12)	40 (12)	40 (8)	90 (10)		35 (16)	41 (13)	87 (16)	

*p-value less than 0.05
#Amongst women with a previous pregnancy

Preterm Delivery

The total estimated incidence of PTD was 18% and was slightly higher in HIV-infected women with normal BMI (22%) compared to those with obese BMI (19%) (Table 2). However, comparison of obese HIV-uninfected and obese HIV-infected women showed a slightly higher PTD incidence (16% vs 19%) in obese HIV-infected women. Overall, adjusted results showed a positive but non-significant association between obese BMI and PTD (aOR 1.06, 95% CI 0.75-1.49) compared to normal BMI (Supplement Table 4) (Appendix 1). When stratifying the analysis by HIV status, adjusted logistic regression results also showed that there was no association between obese BMI and PTD in obese HIV-uninfected women (aOR 1.08, 95% CI 0.66-1.77) and obese HIV-infected participants (aOR 1.02, 95% CI 0.63-1.64) when compared to corresponding women with normal BMI (Table 3). Similarly, restricting the analysis to HIV-infected women by timing of ART initiation also showed no association between PTD and obese BMI and HIV infection in those who initiated ART during (aOR 1.03, 95% CI 0.50-2.11) and before (aOR 1.01, 95% CI 0.53-1.93) pregnancy when compared to corresponding women with normal BMI (Supplement Table 5) (Appendix 1).

Birth Weight

Low Birth Weight: The total estimated incidence of LBW was 12% with obese women having a significantly lower incidence (10%) compared to normal BMI (17%) women (Supplement Table 2). Stratifying by HIV infection also showed a lower LBW incidence in obese compared to normal BMI in HIV-uninfected (8% vs 13%) and HIV-infected (12% vs 21%) women (Table 2). However, between group comparison of obese HIV-uninfected and obese HIV-infected women showed a slightly higher LBW incidence (12% vs 8%) in obese HIV-infected women (Table 2). Restricting the analysis to HIV-infected women by timing of ART initiation and BMI status showed a slightly lower LBW incidence (11% vs 14%) in obese women who initiated ART during pregnancy when compared to corresponding normal BMI women (Supplement Table 3).

Overall adjusted results showed a significant negative association between obese BMI and LBW (aOR 0.53, 95% CI 0.39-0.72) compared to normal BMI (Supplement Table 4) (Appendix 1). When stratifying the analysis by HIV status, adjusted logistic regression results also showed a significant negative association between obese BMI and LBW in obese HIV-uninfected women (aOR 0.51, 95% CI 0.34-0.78) and obese HIV-infected participants (aOR 0.54, 95% CI 0.35-0.83) when compared to corresponding normal BMI women (Table 3). Similarly,

restricting the analysis to HIV-infected women by timing of ART initiation also showed a significant negative association between obese BMI and HIV infection and LBW in those who initiated ART during (aOR 0.51, 95% CI 0.27-0.94) but not statistically significant for those that initiated ART before (aOR 0.56, 95% CI 0.30-1.04) pregnancy when compared to corresponding normal BMI women (Supplement Table 5).

High Birth Weight: The total estimated incidence of HBW is 5% with obese women having a significantly higher incidence (6%) compared to normal BMI (3%) women (Supplement Table 2). Stratifying by HIV infection also showed a higher HBW incidence in obese compared to normal BMI in HIV-uninfected (7% vs 3%) and HIV-infected (5% vs 3%) women compared to corresponding women with normal BMI (Table 2). However, between group comparison of obese HIV-uninfected and obese HIV-infected women showed a slightly lower HBW incidence (7% vs 5%) in obese HIV-infected women (Table 2). Restricting the analysis to HIV-infected women by timing of ART initiation and BMI status showed a higher HBW incidence (7% vs 3%) in obese women who initiated ART during pregnancy when compared to corresponding normal BMI women (Supplement Table 3).

Overall adjusted results showed a significant positive association between obese BMI and HBW (aOR 2.00, 95% CI 1.13-3.57) compared to normal BMI (Supplement Table 4) (Appendix 1). When stratifying the analysis by HIV status, adjusted logistic regression results also showed a significant positive association between obese BMI and HBW in obese HIV-uninfected women (aOR 2.54, 95% CI 1.17-5.53) and a positive but non-significant association in obese HIV-infected participants (aOR 1.41, 95% CI 0.59-3.34) when compared to corresponding normal BMI women (Table 3). Restricting the analysis to HIV-infected women by timing of ART initiation showed a positive but non-significant association between obese BMI and HIV infection and HBW in those who initiated ART during pregnancy (aOR 2.10, 95% CI 0.68-6.48) and a reversed effect in those who initiated ART before (aOR 0.71, 95% CI 0.18-2.83) pregnancy when compared to corresponding normal BMI women (Supplement Table 5).

Size for Gestational Age

Small for Gestational Age: The total estimated incidence of SGA is 12% with obese women having a significantly lower incidence (10%) compared to normal BMI (16%) women (Supplement Table 2). Stratifying by HIV infection also showed a lower SGA incidence in obese compared to normal BMI in HIV-uninfected (8% vs 15%) and HIV-infected (12% vs

18%) women (Table 2). However, between group comparison of obese HIV-uninfected and obese HIV-infected women showed a slightly higher SGA incidence (8% vs 12%) in obese HIV-infected women (Table 2). Restricting the analysis to HIV-infected women by timing of ART initiation and BMI status showed a slightly lower SGA incidence (10% vs 14%) in obese women who initiated ART during pregnancy (Supplement Table 3).

Overall adjusted results showed a significant negative association between obese BMI and SGA (aOR 0.55, 95% CI 0.41-0.75) compared to normal BMI (Supplement Table 4) (Appendix 1). When stratifying the analysis by HIV status, adjusted logistic regression results also showed a significant negative association between obese BMI and SGA in obese HIV-uninfected women (aOR 0.51, 95% CI 0.34-0.78) and in obese HIV-infected participants (aOR 0.60, 95% CI 0.38-0.94) when compared to corresponding normal BMI women (Table 3). Restricting the analysis to HIV-infected women by timing of ART initiation showed a negative but non-significant association between obese BMI and HIV infection and SGA in those who initiated ART during pregnancy (aOR 0.65, 95% CI 0.34-1.26) and a significant negative association in those who initiated ART before (aOR 0.53, 95% CI 0.29-0.99) pregnancy when compared to corresponding normal BMI women (Supplement Table 5).

Large for Gestational Age: The total estimated incidence of LGA is 13% with obese women having a significantly higher incidence (17%) compared to normal BMI (8%) women (Supplement Table 2). Stratifying by HIV infection also showed a higher LGA incidence in obese compared to normal BMI in HIV-uninfected (18% vs 8%) and HIV-infected (14% vs 9%) women (Table 2). However, between group comparison of obese HIV-uninfected and obese HIV-infected women showed a slightly lower LGA incidence (18% vs 14%) in obese HIV-infected women (Table 2). Restricting the analysis to HIV-infected women by timing of ART initiation and BMI status showed a similar LGA incidence (15% vs 14%) in obese women who initiated ART during and before pregnancy when compared to corresponding normal BMI women (Supplement Table 3).

Overall adjusted results showed a significant positive association between obese BMI and LGA (aOR 1.98, 95% CI 1.40-2.80) compared to normal BMI (Supplement Table 4) (Appendix 1). When stratifying the analysis by HIV status, adjusted logistic regression results also showed a significant positive association between obese BMI and LGA in obese HIV-uninfected women (aOR 2.30, 95% CI 1.46-3.62) and a positive but non-significant association in obese HIV-infected participants (aOR 1.58, 95% CI 0.91-2.72) when compared to corresponding normal

BMI women (Table 3). Restricting the analysis to HIV-infected women by timing of ART initiation showed a significant positive association between obese BMI and HIV infection and LGA in those who initiated ART during pregnancy (aOR 3.26, 95% CI 1.32-8.09) and a reversed effect in those who initiated ART before (aOR 0.87, 95% CI 0.43-1.78) pregnancy when compared to corresponding normal BMI women (Supplement Table 5).

Focusing the analysis on the frequencies of SGA and LGA infants provided the summary of the findings shown in Figure 2. Women who are obese only have lower SGA frequency than LGA (Figure 2A), whereas women who are HIV-infected only have the opposite i.e higher SGA than LGA (Figure 2B) when compared to corresponding normal BMI women. Thereby, resulting in obese HIV-infected women to experience a counter effect of both obese BMI and HIV/ART where SGA and LGA frequencies are both high compared to those who have one of the conditions, regardless of ART initiation status (Figure 2C and D).

Table 2. Incidence of adverse birth outcomes by BMI and HIV status among women with live singleton births (n = 2779)

	HIV-uninfected n = 1699				**HIV-infected n = 1080**			
	BMI				**BMI**			
	Normal n = 336	Overweight n = 492	Obese n = 871	Chi^2 p-value	Normal n = 220	Overweight n = 315	Obese n = 545	Chi^2 p-value
GA (weeks)				0.173				0.321
Preterm (<37)	56 (17)	89 (18)	143 (16)		49 (22)	52 (17)	105 (19)	
Term (≥37)	272 (81)	387 (79)	716 (82)		167 (76)	259 (82)	436 (80)	
Missing	8 (2)	16 (3)	12 (1)		4 (2)	4 (1)	4 (0.7)	
Birth weight (g)				0.001*				0.005*
Low (<2500)	45 (13)	58 (12)	71 (8)		47 (21)	34 (11)	75 (12)	
Normal (2500 - 3999)	281 (84)	417 (85)	743 (85)		165 (75)	269 (85)	448 (82)	
High (≥4000)	9 (3)	17 (3)	57 (7)		7 (3)	8 (2.5)	27 (5)	
Mean (SD)	3049 (543)	3115 (590)	3256 (555)		2891 (623)	3081 (531)	3126 (591)	
Missing	1 (0.3)	0	0		1 (0.5)	4 (1)	4 (0.7)	
Size for GA				<0.001*				0.024*
Small (<10^{th})	50 (15)	59 (12)	70 (8)		40 (18)	59 (19)	65 (12)	
Appropriate (10-90^{th})	237 (71)	333 (68)	598 (69)		153 (70)	216 (69)	381 (70)	
Large (>90^{th})	27 (8)	61 (12)	159 (18)		19 (9)	28 (9)	77 (14)	
Missing	22 (7)	39 (8)	44 (5)		8 (4)	12 (4)	22 (4)	

*p-value less than 0.05

Table 3. Adjusted odds of adverse birth outcomes by HIV status among women with high BMI compared to normal BMI (n = 2779).

	HIV-uninfected n = 1699				**HIV-infected n = 1080**			
	BMI				**BMI**			
	Overweight n = 492		Obese n = 871		Overweight n = 315		Obese n = 545	
	aOR (95% CI)	p-value	aOR (95% CI)	p-value	aOR (95% CI)	p-value	aOR (95% CI)	p-value
GA (weeks)								
Preterm (<37)	0.88 (0.52-1.50)	0.641	1.08 (0.66-1.77)	0.762	1.26 (0.74-2.17)	0.394	1.02 (0.63-1.64)	0.942
Birth weight (g)								
Low (<2500)	0.82 (0.53-1.25)	0.358	0.51 (0.34-0.78)	0.002*	0.46 (0.28-0.76)	0.002*	0.54 (0.35-0.83)	0.005*
High (≥4000)	1.35 (0.57-3.21)	0.501	2.54 (1.17-5.53)	0.019*	0.70 (0.25-2.00)	0.508	1.41 (0.59-3.34)	0.440
Size for GA								
Small (<10^{th})	0.81 (0.54-1.24)	0.336	0.51 (0.34-0.78)	0.002*	0.92 (0.58-1.46)	0.721	0.60 (0.38-0.94)	0.026*
Large (>90^{th})	1.55 (0.95-2.53)	0.077	2.30 (1.46-3.62)	<0.001*	1.01 (0.54-1.88)	0.987	1.58 (0.91-2.72)	0.103

*p-value less than 0.05
aOR – Odds ratio

Preterm model – logistic regression: adjusted for maternal age, GA at enrolment, parity, prior PTD, ART status

Birth weight model – multinomial logistic regression: adjusted for maternal age, GA at enrolment, parity, ART status

Size for GA model – multinomial logistic regression: adjusted for maternal age, GA at enrolment, parity, ART status

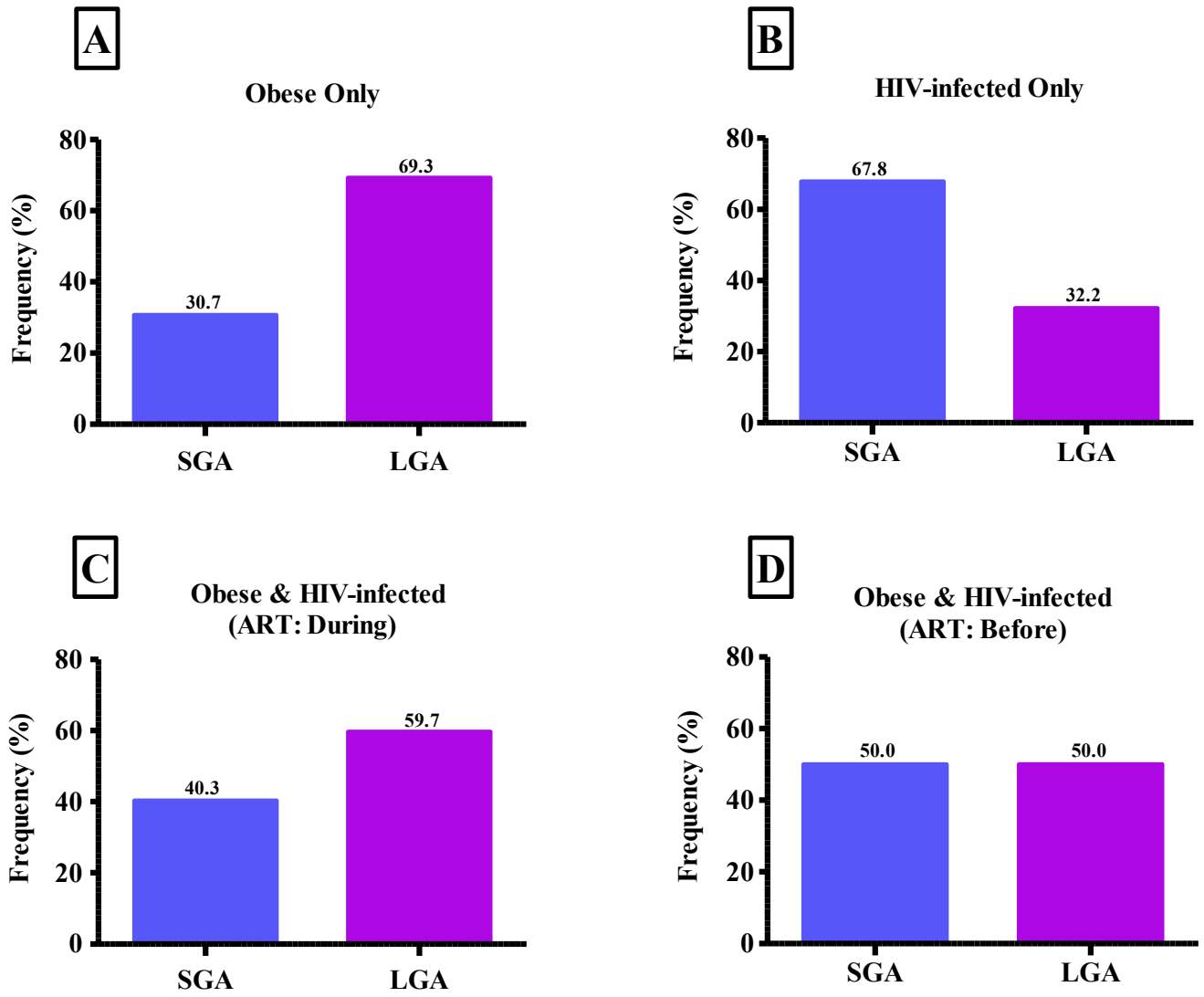

Figure 2. Comparison of frequencies of SGA and LGA infants within groups: women who are obese only (A), HIV-infected only (B), obese HIV-infected with ART initiation during pregnancy (C) and obese HIV-infected with ART initiation before pregnancy (D).

3.2 Assessment B

A total of 364 HIV-infected women with live singleton births were included. Obese HIV-infected women were more likely to be older, not complete high school, have higher gravidity, parity and previous pregnancy losses compared to normal BMI women (Supplement Table 6). Although most women gained lower weight than recommended by IOM, obese women gained higher than recommended compared to normal BMI women (19% vs 4%) (Supplement Table 7). Adjusted logistic regression results showed a positive but non-significant association between low GWG and PTD (aOR 1.37, 95% CI 0.39-4.82) and negative but non-significant association with high GWG (aOR 0.45, 95% CI 0.09-2.24) compared to adequate GWG (Table 4).

With regards to birth weight, women with low GWG had a higher incidence of LBW (12%) compared to those with adequate (8%) and high GWG (7%) (Supplement Table 8). Adjusted logistic regression results showed a positive but non-significant association between low GWG and LBW (aOR 1.49, 95% CI 0.61-3.63) and negative but non-significant association with high GWG (aOR 0.86, 95% CI 0.20-3.64) compared to adequate GWG (Table 4). On the other hand, women with low GWG had a lower incidence of HBW (3%) compared to those with adequate (8%) and high GWG (5%) (Supplement Table 8). Adjusted logistic regression results showed a significant negative association between HBW and low GWG (aOR 0.26, 95% CI 0.08-0.84) but non-significant association with high GWG (aOR 0.67, 95% CI 0.12-3.62) compared to adequate GWG (Table 4).

With regards to size for gestational age, women with low GWG had a higher incidence of SGA (17%) compared to those with adequate (12%) and high GWG (14%) (Supplement Table 8). Adjusted logistic regression results showed a positive but non-significant association between low GWG and SGA (aOR 1.31, 95% CI 0.61-2.80) and between high GWG and SGA (aOR 1.17, 95% CI 0.38-3.57) compared to adequate GWG (Table 4). On the other hand, women with low GWG had a lower incidence of LGA (5%) compared to those with adequate (15%) and high GWG (11%) (Supplement Table 8). Adjusted logistic regression results showed a significant negative association between low GWG and LGA (aOR 0.29, 95% CI 0.12-0.70) but non-significant association in women with high GWG (aOR 0.85, 95% CI 0.27-2.74) compared to adequate GWG (Table 4).

Table 4. Multivariate association of adverse birth outcomes with low and high GWG compared to adequate GWG among HIV-infected women (n = 364).

	Total (n = 364)			
	GWG			
	Low n = 235		High n = 44	
	aOR (95% CI)	p-value	aOR (95% CI)	p-value
GA (weeks)				
Preterm (<37)	1.37 (0.39-4.82)	0.626	0.45 (0.09-2.24)	0.332
Birth weight (g)				
Low (<2500)	1.49 (0.61-3.63)	0.381	0.86 (0.20-3.64)	0.838
High (≥4000)	0.26 (0.08-0.84)	0.024*	0.67 (0.12-3.62)	0.640
Size for GA				
Small (<10th)	1.31 (0.61-2.80)	0.482	1.17 (0.38-3.57)	0.787
Large (>90th)	0.29 (0.12-0.70)	0.006*	0.85 (0.27-2.74)	0.790

*p-value less than 0.05
aOR – Odds ratio

Preterm model – logistic regression: adjusted for maternal age, education, GA at enrolment, parity, prior PTD, ART status

Birth weight model – multinomial logistic regression: adjusted for maternal age, education, GA at enrolment, parity, ART status

Size for GA model – multinomial logistic regression: adjusted for maternal age, education, GA at enrolment, parity, ART status

4. DISCUSSION

This study investigated the association between high BMI/GWG and adverse birth outcomes by HIV and ART status in South African women seeking ANC services at Gugulethu MOU. Our data shows high prevalence of obesity (51%) amongst HIV-uninfected and HIV-infected women. This prevalence suggests that obesity in South Africa is on the rise when compared to the 33.1% found in a similar cohort from another peri-urban area in Cape Town 8 years ago (38). In addition, we found high obesity prevalence of 50% in HIV-infected women, supporting the growing evidence that suggests increased obesity prevalence amongst HIV-infected women, which now mirrors that in the general population (39-41).

Although other scholars reported high risk of PTD in women with obese BMI, particularly medically-indicated PTD (20, 22, 42, 43); in this study we found no association by both HIV and ART status (Table 3 and Supplement Table 5). These scholars suggest that pre-pregnancy conditions such as diabetes and hypertension are responsible for this association. In contrast, most women in our cohort delivered at the MOU (66%), a primary care facility operated by midwives; indicating that they had no history of medical complications. Our findings are in agreement with those reported by Ajen et al.(44) which found no association between obese BMI and PTD in the Nigerian cohort. Nonetheless, the PTD incidence (18%) we found was higher than the estimated population average of 10% in South Africa (45).

The majority of our women did not meet the IOM recommended guidelines for weight gain. Our data shows that both low and high GWG had no association with PTD in HIV-infected women. However, other studies found that low and high GWG is associated with PTD (22, 46). The three GWG categories of low, adequate and high used in this study are based on IOM ranges which are linked to pre-pregnancy BMI (35, 47, 48). The absence of an association in our cohort may be due to the small sample size for the subset of women that were used for GWG analysis. However, there has been controversy regarding the applicability of IOM guidelines for GWG in African setting as they were formulated using data obtained from US population (35, 49, 50).

With regards to birth weight, overall obese BMI was significantly associated with reduced likelihood of having LBW and SGA infants as also seen elsewhere (19, 20, 51). Similar effect was observed for obese HIV-infected women though to a lesser extent when compared to obese HIV-uninfected women (Table 2). These findings were expected because one of the

mechanisms for LBW and SGA infants in pregnant women that have been proposed by other authors is poor maternal nutrition resulting in insufficient nutrients available to the foetus and poor development (21, 52). Considering that obesity is a condition characterised by excessive accumulation of body fat, it is reasonable to speculate that women with obese BMI are not likely to lack nutrients needed for foetal development. Although many studies have reported HIV infection and/or ART use in pregnancy to be associated with LBW/SGA (28, 30, 53-55), only one study has investigated the combined impact of both obesity and HIV infection on adverse birth outcomes.

In that study Anderson et al.(56) found increased incidence of LBW infants in obese HIV-infected women compared to obese HIV-uninfected women as was also observed in this current study (Table 2). However, in Anderson et al study, the population was that of women from an area with highly ambient air polluted which may have confounded the association (57). In addition, in our study we further showed that obese women who initiated ART during pregnancy have a lower incidence of LBW/SGA compared to those who initiated before pregnancy. These findings are also plausible and in agreement with those found in the Botswana cohort where women who initiated ART before pregnancy had worse outcomes compared to those who recently initiated ART during pregnancy (27). The mechanism of LBW/SGA induced by long term use of ART was proposed in a study which found that high doses of tenofovir *in utero* reduces levels of insulin-like growth factor-1 (IGF-1) and restrict intrauterine growth (58, 59). Therefore, the higher incidence of LBW/SGA observed in obese HIV-infected women was probably due to LBW promoting effects of ART in those that initiated ART before pregnancy. Interestingly, growing evidence suggests that LBW/SGA infants tend to undergo 'catch up growth' in early life which increases the risk of developing obesity, type 2 diabetes and cardiovascular diseases later in life (60-64).

The total incidence of HBW, also referred to as macrosomia was 5% in our study, this is higher than the previously reported prevalence of 3.4% in South Africa (65) and from other African countries (66, 67). This increase may be partly attributed to a significant increase in obesity prevalence. In support of this, our findings show that women with obese BMI are almost twice as likely to have macrosomic and LGA infants compared to normal BMI women (Table 3) as reported in other studies conducted in Africa (11, 13, 68, 69). Although this association remained positive in obese HIV-infected women, it was to a lesser extent compared to obese HIV-uninfected women, possibly due to the opposite impact of HIV infection/ART-use on birth

weight (28, 30, 53-55). This was also reflected when we restricted the analysis to HIV-infected women by timing of ART initiation; obese women who initiated ART during pregnancy were more likely to have LGA infants compared to those who initiated ART before pregnancy (Supplement Table 5), corroborating the implicated birth weight-lowering effect of long term ART use in those that initiated ART before pregnancy (Figure 2D). Although there seem to be differences in the risks of SGA and LGA infants by ART initiation status where initiating ART before pregnancy increases the risk of SGA and initiating ART during pregnancy increases the risk of LGA, focusing the analysis to SGA and LGA frequencies in different groups of women shows a high risk of both morbidities in obese women, regardless of ART initiation status (Figure 2).

Our findings regarding the positive association between obese BMI and macrosomia and LGA in HIV-uninfected and HIV-infected women are parallel to those of other authors (7, 8, 33, 67, 70). Although we did not measure maternal glucose and lipids, the previously proposed mechanism for the influence of maternal obesity on foetal growth is gestational diabetes mellitus characterised by insulin resistance which leads to increased maternal glucose and triglycerides (71). Since maternal blood is passed to the foetus via the placenta, the foetus also experiences high levels of insulin, glucose and triglycerides which all promote foetal overgrowth (72-74). Macrosomic/LGA infants are likely to become obese in their childhood and this predisposes them to diabetes mellitus and metabolic syndrome (15-17).

Although other studies report that high GWG increase the likelihood of having a macrosomic or LGA infants, this was not observed in our study, probably due to the small sample size for the subset of women in which this analysis was performed. However, we showed that HIV-infected women with low gestational weight gain are less likely to have LGA infants compared to those who gained the recommended weight (Table 4). This result is similar to the findings that were reported by Vesco et al. (75) in HIV-uninfected women. Exclusion of 12% and 21% of women that had missing data for BMI and GWG (21% participants who did not have weight measurement at the third trimester visit, some of them due to early delivery before their third trimester study visit), respectively, may have resulted in selection bias and therefore our findings should be interpreted with caution. In addition, absence of broader demographic information such as education and SES for the overall cohort poses a potential for unmeasured confounding in our results. Our investigations were conducted in a cohort of women presenting for first ANC visit at varying gestations and therefore we could not measure pre-pregnancy

BMI. However, for the longitudinal subset cohort of HIV-infected women, we obtained first trimester BMI because of the study design. First trimester BMI is considered a proxy for pre-pregnancy BMI as weight change in early pregnancy is negligible (76, 77). Using the subset cohort as a comparison group, we conducted sensitivity analysis to assess the extent of exaggeration of BMI distribution in the overall cohort. We found that restricting the analysis of baseline BMI distribution by trimester at first ANC visit in the overall cohort provides similar baseline BMI prevalence as the subset cohort. Therefore, our findings are meaningful and they reflect the challenge of late presentation for first ANC visit in our setting, which needs to be considered when designing interventions targeted at minimising GWG to avert adverse birth outcomes.

5. CONCLUSION

In overall, our results show negative association between high BMI and LBW and SGA when compared to normal BMI women regardless of HIV status. However, this effect should not be considered as entirely positive because it is paralled by an adverse outcome of HBW and LGA infants. Besides, a closer look at obese HIV-infected women shows a burden of both LBW/SGA and LGA, regardless of ART initiation status. Therefore, HIV care programs need to incorporate management strategies for women with high body mass index to minimise adverse infant outcomes.

Competing Interests

The authors declare that there are no conflicting interests.

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PART D: APPENDICES

1. MANUSCRIPT SUPPLEMENTAL MATERIAL

Table 1a. Maternal baseline characteristics of enrolled participants with live singleton births by BMI (n = 2779)

		BMI (n = 2779)			
	Total n = 2779	**Normal n = 556**	**Overweight n = 807**	**Obese n = 1416**	***Chi²* *p- value***
Age (years)					<0.001*
<20	273 (10)	102 (18)	99 (12)	72 (5)	
20-24	604 (22)	158 (28)	196 (24)	250 (18)	
25-29	786 (28)	150 (17)	227 (28)	409 (29)	
30-34	700 (25)	113 (20)	191 (24)	396 (28)	
≥35	416 (15)	33 (6)	94 (12)	289 (20)	
Median (IQR)	28 (23-32)	25 (21-30)	27 (23-32)	29 (25-34)	
Height (cm)					0.363
≤155	939 (34)	177 (32)	263 (33)	499 (35)	
156-161	1053 (38)	217 (39)	300 (37)	536 (38)	
≥162	787 (28)	162 (29)	244 (30)	381 (27)	
Median (IQR)	158 (154-162)	158 (155-162)	158 (154-163)	158 (154-162)	
Obstetric					
GA (weeks)					0.002*
1st trimester (≤13)	712 (26)	156 (28)	187 (23)	369 (26)	
2nd trimester (14-28)	1598 (58)	330 (59)	469 (58)	799 (56)	
3rd trimester (>28)	406 (15)	53 (10)	129 (16)	224 (16)	
Median (IQR)	19 (13-25)	18 (13-23)	20 (14-26)	20 (13-25)	
Missing	63 (2)	17 (3)	22 (3)	24 (2)	
Gravidity					<0.001*
1	673 (24)	202 (36)	226 (28)	245 (17)	
2	951 (34)	197 (35)	281 (35)	473 (33)	
≥3	1148 (41)	155 (28)	298 (37)	695 (49)	
Median (IQR)	2 (2-3)	2 (1-3)	2 (1-3)	2 (2-3)	
Missing	7 (0.3)	2 (0.4)	2 (0.3)	3 (0.2)	
Parity					<0.001*
0	822 (30)	252 (45)	274 (34)	296 (21)	
1	1038 (37)	194 (35)	291 (36)	553 (39)	
≥2	911 (33)	108 (19)	240 (30)	563 (40)	
Median (IQR)	1 (0-2)	1 (0-1)	1 (0-2)	1 (1-2)	
Missing	8 (0.3)	2 (0.4)	2 (0.3)	4 (0.3)	
Prior preterm#					<0.001*
Yes	200 (7)	36 (6)	57 (7)	107 (8)	
No	1684 (61)	255 (46)	468 (58)	961 (68)	
Missing	895 (32)	265 (48)	282 (35)	348 (25)	
Prior pregnancy loss#					<0.001*
Yes	333 (12)	75 (13)	81 (10)	177 (13)	
No	1645 (59)	252 (45)	469 (58)	924 (65)	
Missing	801 (29)	229 (41)	257 (32)	315 (22)	

*p-value less than 0.05

#Among women with a previous pregnancy

Table 1b. Maternal baseline characteristics of enrolled HIV-infected participants with live singleton births by BMI and ART status (n =1080)

		ART initiation during pregnancy n = 541				ART initiation before pregnancy n = 539			
		BMI				BMI			
	Total n = 1080	Normal n = 120	Overweight n = 146	Obese n = 275	Chi^2 p-value	Normal n = 100	Overweight n = 169	Obese n = 270	Chi^2 p-value
Age (years)					<0.001*				0.004*
<20	53 (5)	9 (8)	14 (10)	14 (5)		7 (7)	4 (2)	5 (2)	
20-24	155 (14)	34 (28)	16 (11)	38 (14)		12 (12)	30 (18)	25 (9)	
25-29	304 (28)	41 (34)	48 (33)	95 (35)		28 (28)	36 (21)	56 (21)	
30-34	357 (33)	33 (28)	49 (34)	89 (32)		36 (36)	56 (33)	94 (35)	
≥35	211 (20)	3 (3)	19 (13)	39 (14)		17 (17)	43 (25)	90 (33)	
Median (IQR)	30 (25-33)	26 (23-30)	29 (25-32)	29 (25-32)		30 (25-33)	31 (26-35)	32 (28-35)	
Height (cm)					0.032*				0.960
≤155	364 (34)	33 (28)	43 (29)	112 (41)		36 (36)	53 (31)	87 (32)	
156-161	366 (34)	35 (29)	52 (36)	82 (30)		34 (34)	63 (37)	100 (37)	
≥162	311 (29)	42 (35)	44 (30)	72 (26)		28 (28)	50 (30)	75 (28)	
Median (IQR)	158 (154-163)	159 (154-163)	158 (154-163)	157 (153-162)		158 (154-163)	159 (154-162)	158 (154-162)	
Missing	39 (4)	10 (8)	7 (5)	9 (3)		2 (2)	3 (2)	8 (2)	
Obstetrics									
GA (weeks)					0.157				0.582
1st trimester (≤13)	331 (31)	35 (29)	27 (18)	75 (27)		37 (37)	60 (36)	97 (36)	
2nd trimester (14-28)	578 (54)	67 (56)	88 (60)	151 (56)		51 (51)	83 (49)	138 (51)	
3rd trimester (>28)	144 (13)	12 (10)	26 (18)	43 (43)		9 (9)	25 (15)	29 (11)	
Median (IQR)	18 (12-25)	18 (12-22)	20 (15-27)	19 (13-25)		17 (12-20)	18 (12-25)	17 (12-24)	
Missing	27 (3)	6 (5)	5 (3)	6 (2)		3 (3)	1 (1)	6 (2)	
Gravidity					<0.001*				0.436
1	181 (17)	34 (28)	32 (22)	37 (13)		17 (17)	30 (18)	31 (11)	
2	375 (35)	53 (44)	46 (32)	96 (35)		36 (36)	56 (33)	88 (33)	
≥3	518 (48)	32 (27)	67 (46)	141 (51)		46 (46)	82 (49)	150 (56)	
Median (IQR)	2 (2-3)	2 (1-3)	2 (2-3)	3 (2-3)		2 (2-3)	2 (2-3)	3 (2-3)	
Missing	6 (1)	1 (1)	1 (1)	1 (0.4)		1 (1)	1 (1)	1 (0.4)	
Parity					0.001*				0.033*
0	242 (22)	44 (37)	37 (25)	49 (18)		25 (25)	45 (27)	42 (16)	
1	427 (40)	51 (43)	53 (36)	119 (43)		43 (43)	53 (31)	108 (40)	
≥2	404 (37)	24 (20)	55 (38)	105 (38)		31 (31)	70 (41)	119 (44)	
Median (IQR)	1 (1-2)	1 (0-1)	1 (0-2)	1 (1-2)		1 (0-2)	1 (0-2)	1 (1-2)	
Missing	7 (1)	1 (1)	1 (1)	2 (1)		1 (1)	1 (1)	1 (0.4)	
Prior preterm#					0.026*				0.538
Yes	94 (9)	13 (10)	13 (9)	20 (7)		8 (8)	17 (10)	23 (9)	
Prior pregnancy loss#					0.115				0.353
Yes	163 (15)	14 (12)	18 (12)	47 (17)		21 (21)	23 (14)	40 (15)	

*p-value less than 0.05
#Amongst women with a previous pregnancy

Table 2. Incidence of adverse birth outcomes by BMI among women with live singleton births (n = 2779)

	Total n = 2779	BMI (n = 2779) Normal n = 556	Overweight n = 807	Obese n = 1416	Chi^2 p-value
GA (weeks)					0.138
Preterm (<37)	494 (18)	105 (19)	141 (17)	248 (18)	
Term (≥37)	2237 (81)	439 (79)	646 (80)	1152 (81)	
Missing	48 (2)	12 (2)	20 (2)	16 (1)	
Birth weight (g)					<0.001*
Low (<2500)	321 (12)	92 (17)	92 (11)	137 (10)	
Normal (2500 - 3999)	2323 (84)	446 (80)	686 (85)	1191 (84)	
High (≥4000)	125 (5)	16 (3)	25 (3)	84 (6)	
Mean (SD)	3132 (578)	2987 (580)	3102 (567)	3206 (572)	
Missing	10 (0.4)	2 (0.4)	4 (0.5)	4 (0.3)	
Size for GA					<0.001*
Small (<10^{th})	343 (12)	90 (16)	118 (15)	135 (10)	
Appropriate (10-90^{th})	1918 (69)	390 (90)	549 (68)	979 (69)	
Large (>90^{th})	371 (13)	46 (8)	89 (11)	236 (17)	
Missing	147 (5)	30 (5)	51 (6)	66 (5)	

Table 3. Incidence of adverse birth outcomes by BMI and ART status among HIV-infected women with live singleton births (n = 1080)

	HIV-infected n =1080							
	ART initiation during pregnancy n = 541				ART initiation before pregnancy n = 539			
	BMI				BMI			
	Normal n = 120	Overweight n = 146	Obese n = 275	Chi^2 p-value	Normal n = 100	Overweight n = 169	Obese n = 270	Chi^2 p-value
GA (weeks)				0.363				0.420
Preterm (<37)	27 (23)	27 (18)	46 (17)		22 (22)	25 (15)	59 (22)	
Term (≥37)	90 (75)	116 (79)	227 (83)		77 (77)	143 (85)	209 (77)	
Missing	3 (2.5)	3 (2)	2 (0.7)		1 (1)	1 (1)	2 (1)	
Birth weight (g)				0.021*				0.129
Low (<2500)	26 (22)	20 (14)	29 (11)		21 (21)	14 (8)	37 (14)	
Normal (2500 - 3999)	90 (75)	121 (83)	224 (81)		75 (75)	148 (88)	224 (83)	
High (≥4000)	4 (3)	3 (2)	19 (7)		3 (3)	5 (3)	8 (3)	
Mean (SD)	2868 (631)	3058 (589)	3182 (612)		2919 (615)	3101 (475)	3070 (564)	
Missing	0	2 (1)	3 (1)		1 (1)	2 (1)	1 (0.4)	
Size for GA				0.027*				0.412
Small (<10^{th})	18 (15)	27 (18)	28 (10)		22 (22)	32 (19)	37 (14)	
Appropriate (10-90^{th})	91 (76)	103 (71)	196 (71)		62 (62)	113 (67)	185 (69)	
Large (>90^{th})	6 (5)	12 (8)	40 (15)		13 (13)	16 (9)	37 (14)	
Missing	5 (4)	4 (3)	11 (4)		3 (3)	8 (5)	11 (4)	

*p-value less than 0.05

Table 4. Adjusted odds of adverse birth outcomes among women with high BMI compared to normal BMI (n = 2779)

	BMI			
	Overweight n = 807		Obese n = 1416	
	aOR (95% CI)	p-value	aOR (95% CI)	p-value
GA (weeks)				
Preterm (<37)	1. 05 (0.72-1.52)	0.814	1.06 (0.75-1.49)	0.739
Birth weight (g)				
Low (<2500)	0.64 (0.47-0.89)	0.008*	0.53 (0.39-0.72)	<0.001*
High (≥4000)	1.03 (0.53-1.99)	0.932	2.00 (1.13-3.57)	0.018*
Size for GA				
Small (<10th)	0.87 (0.64-1.18)	0.373	0.55 (0.41-0.75)	<0.001*
Large (>90th)	1.33 (0.91-1.95)	0.141	1.98 (1.40-2.80)	<0.001*

*p-value less than 0.05

Preterm model – logistic regression: adjusted for maternal age, GA at enrolment, parity, prior PTD, HIV infection

Birth weight model – multinomial logistic regression: adjusted for maternal age, GA at enrolment, parity, HIV infection

Size for GA model – multinomial logistic regression: adjusted for maternal age, GA at enrolment, parity, HIV infection

Table 5. Adjusted odds of adverse birth outcomes by ART status among HIV-infected women with high BMI compared to normal BMI (n = 1080)

	HIV-infected n = 1080							
	ART initiation during pregnancy n = 541				**ART initiation before pregnancy n = 539**			
	BMI				**BMI**			
	Overweight n = 146		Obese n = 275		Overweight n = 169		Obese n = 270	
	aOR (95% CI)	p-value	aOR (95% CI)	p-value	aOR (95% CI)	p-value	aOR (95% CI)	p-value
GA (weeks)								
Preterm (<37)	0.79 (0.36-1.73)	0.551	1.03 (0.50-2.11)	0.937	1.94 (0.91-4.13)	0.088	1.01 (0.53-1.93)	0.979
Birth weight (g)								
Low (<2500)	0.65 (0.33-1.30)	0.225	0.51 (0.27-0.94)	0.032*	0.33 (0.15-0.69)	0.003*	0.56 (0.30-1.04)	0.067
High (≥4000)	0.65 (0.14-3.03)	0.582	2.10 (0.68-6.48)	0.194	0.70 (0.16-3.07)	0.635	0.71 (0.18-2.83)	0.627
Size for GA								
Small (<10th)	1.12 (0.57-2.22)	0.737	0.65 (0.34-1.26)	0.201	0.74 (0.39-1.39)	0.349	0.53 (0.29-0.99)	0.047*
Large (>90th)	1.89 (0.67-5.31)	0.229	3.26 (1.32-8.09)	0.011*	0.64 (0.29-1.43)	0.276	0.87 (0.43-1.78)	0.710

*p-value less than 0.05

Preterm model – logistic regression: adjusted for maternal age, GA at enrolment, parity, prior PTD

Birth weight model – multinomial logistic regression: adjusted for maternal age, GA at enrolment, parity

Size for GA model – multinomial logistic regression: adjusted for maternal age, GA at enrolment, parity

All outcomes adjusted for maternal age, height, GA at enrolment, parity, prior PTD

Table 6. Maternal baseline characteristics of HIV-infected women with live singleton births by BMI (n = 364)

	Total n = 364	**BMI**			Chi^2 p-value
		Normal n = 91	Overweight n = 107	Obese n = 166	
Age (years)					0.224
<20	16 (4)	5 (5)	5 (5)	6 (4)	
20-24	46 (13)	16 (18)	15 (14)	15 (9)	
25-29	110 (30)	33 (36)	32 (30)	45 (27)	
30-34	110 (30)	23 ()25	32 (30)	55 (33)	
≥35	82 (23)	14 (15)	23 (22)	45 (27)	
Median (IQR)	30 (26-34)	28 (25-33)	30 (26-33)	31 (28-35)	
In a relationship					0.800
Yes	356 (98)	88 (97)	106 (99)	162 (98)	
No	6 (2)	2 (2)	1 (1)	3 (2)	
Missing	2 (0.5)	1 (1)	0	1 (0.6)	
Completed High School					0.239
Yes	100 (27)	30 (33)	30 (28)	40 (24)	
No	263 (72)	60 (66)	77 (72)	126 (76)	
Missing	1 (0.3)	1 (1)	0	0	
Employed					0.914
Yes	161 (44)	39 (43)	49 (46)	73 (44)	
No	203 (56)	52 (57)	58 (54)	93 (56)	
Height (cm)					0.476
≤155	86 (24)	21 (23)	27 (25)	38 (23)	
156-161	141 (39)	36 (40)	34 (32)	71 (43)	
≥162	137 (38)	34 (37)	46 (43)	57 (34)	
Median (IQR)	160 (156-164)	160 (156-165)	161 (156-165)	160 (156-163)	
GA at enrolment (weeks)					
Median (IQR)	15 (12-18)	15 (12-18)	15 (12-18)	14 (11-18)	0.633
Gravidity					0.004*
1	66 (18)	25 (27)	18 (17)	23 (14)	
2	126 (35)	36 (40)	41 (38)	49 (30)	
≥3	172 (47)	30 (33)	48 (45)	94 (57)	
Median (IQR)	2 (2-3)	2 (1-3)	2 (2-3)	3 (2-3)	
Parity					0.029*
0	90 (25)	33 (36)	25 (23)	32 (19)	
1	159 (44)	38 (42)	46 (43)	75 (45)	
≥2	115 (32)	20 (22)	36 (34)	59 (36)	
Median (IQR)	1 (1-2)	1 (0-1)	1 (1-2)	1 (1-2)	
Prior preterm[#]					0.190
Yes	32 (9)	9 (10)	8 (7)	15 (9)	
Prior pregnancy loss[#]					0.025*
Yes	69 (19)	11 (12)	15 (14)	43 (26)	

*p-value less than 0.05;

#Among women with a previous pregnancy

Table 7. Proportion of HIV-infected women with low, adequate and high GWG within each BMI category based on IOM's GWG guidelines (n = 364)

	IOM GWG guidelines Total (kg)	**GWG (n = 364)**			Chi^2 p-value
		Low n = 235	Adequate n = 85	High n = 44	
BMI (kg/m^2)					<0.001*
Normal (18.5-24.9)	11.5 – 16	76 (84)	11 (12)	4 (4)	
Overweight (25-29.9)	7 – 11.5	69 (64)	29 (27)	9 (8)	
Obese (≥30)	5-9	90 (54)	45 (27)	31 (19)	

Table 8. Incidence of adverse birth outcomes by GWG among HIV-infected women with live singleton births (n = 364)

		Total n = 364			Chi^2 p-value
		GWG			
	Total n = 364	Low n = 235	Adequate n = 85	High n = 44	
GA (weeks)					0.902
Preterm (<37)	27 (7)	17 (7)	6 (7)	4 (9)	
Term (≥37)	337 (93)	218 (93)	79 (93)	40 (91)	
Birth weight (g)					
Low (<2500)	39 (11)	29 (12)	7 (8)	3 (7)	0.253
Normal (2500 - 3999)	308 (85)	198 (84)	71 (84)	39 (89)	
High (≥4000)	15 (4)	6 (3)	7 (8)	2 (5)	
Mean (SD)	3122 (508)	3062 (495)	3264 (512)	3160 (522)	
Missing	2 (0.5)	2 (1)	0	0	
Size for GA					0.025*
Small (<10th)	57 (16)	41 (17)	10 (12)	6 (14)	
Appropriate (10-90th)	278 (76)	183 (78)	62 (73)	33 (75)	
Large (>90th)	29 (8)	11 (5)	13 (15)	5 (11)	

*p-value less than 0.05

2. ETHICS APPROVAL DOCUMENTS

2A. UCT Ethics Approval of Current Study

UNIVERSITY OF CAPE TOWN
Faculty of Health Sciences
Human Research Ethics Committee

Room E53-48 Old Main Building
Groote Schuur Hospital
Observatory 7925
Telephone (021) 406 6492
Email: sumayah.arieff@uct.ac.za
Website: www.health.uct.ac.za/fhs/research/humanethics/forms

04 June 2018

HREC REF: 350/2018

Prof L Myer
Division Epidemiology & Biostatistics
Office 5.51, Level 5
Falmouth Building-FHS

Dear Prof Myer

PROJECT TITLE: ASSOCIATION BETWEEN HIGH BODY MASS INDEX AND ADVERSE BIRTH OUTCOMES IN HIV-INFECTED SOUTH AFRICAN WOMEN, CAPE TOWN (MASTERS CANDIDATE - DR HP. Madlala)

Thank you for submitting your study to the Faculty of Health Sciences Human Research Ethics Committee (HREC) for review.

It is a pleasure to inform you that the HREC has **formally approved** the above-mentioned study.

Approval is granted for one year until the 30 June 2019.

Please submit a progress form, using the standardised Annual Report Form if the study continues beyond the approval period. Please submit a Standard Closure form if the study is completed within the approval period.
(Forms can be found on our website: www.health.uct.ac.za/fhs/research/humanethics/forms)

We acknowledge that the student: Dr Hlengiwe Madlala will also be involved in this study.

Please quote the HREC REF in all your correspondence.

Please note that the ongoing ethical conduct of the study remains the responsibility of the principal investigator.

Please note that for all studies approved by the HREC, the principal investigator **must** obtain appropriate institutional approval before the research may occur.
Yours sincerely

PROFESSOR M BLOCKMAN
CHAIRPERSON, FHS HUMAN RESEARCH ETHICS COMMITTEE

Federal Wide Assurance Number: FWA00001637.
Institutional Review Board (IRB) number: IRB00001938

2B. UCT Ethics Approval of Parent Study

UNIVERSITY OF CAPE TOWN
Faculty of Health Sciences
Human Research Ethics Committee

Room E52-24 Old Main Building
Groote Schuur Hospital
Observatory 7925
Telephone [021] 406 6338 • **Facsimile** [021] 406 6411
Email: shuretta.thomas@uct.ac.za
Website: www.health.uct.ac.za/fhs/research/humanethics/forms

30 October 2014

HREC REF: 739/2014

A/Prof L Myer
Epidemiology & Biostatistics
Public Health & Family Medicine
Falmouth Building
Level 5, entrance 5

Dear A/Prof Myer

PROJECT TITLE: ANTIRETROVIRAL THERAPY AND RISK OF PREMATURE DELIVERY: THE PREMATURITY IMMUNOLOGY IN HIV-INFECTED MOTHERS AND THEIR INFANTS STUDY (PIMS)

Thank you for your response to the Faculty of Health Sciences Human Research Ethics Committee dated 28 October 2014.

It is a pleasure to inform you that the HREC has **formally approved** the above-mentioned study.

Approval is granted for one year until the 30th October 2015.

Please submit a progress form, using the standardised Annual Report Form if the study continues beyond the approval period. Please submit a Standard Closure form if the study is completed within the approval period.
(Forms can be found on our website: www.health.uct.ac.za/fhs/research/humanethics/forms)

Please quote the HREC REF in all your correspondence.

Please note that the ongoing ethical conduct of the study remains the responsibility of the principal investigator.

Yours sincerely

PROFESSOR M BLOCKMAN
CHAIRPERSON, FHS HUMAN RESEARCH ETHICS COMMITTEE
Federal Wide Assurance Number: FWA00001637.
Institutional Review Board (IRB) number: IRB00001938
This serves to confirm that the University of Cape Town Human Research Ethics Committee complies to the Ethics Standards for Clinical Research with a new drug in patients, based on the Medical Research Council (MRC-SA), Food and Drug Administration (FDA-USA), International Convention on Harmonisation Good Clinical Practice (ICH GCP) and Declaration of Helsinki guidelines.

HREC 739/2014

2C. Southampton Ethics Approval of Parent Study

Medicine

UNIVERSITY OF Southampton

Professor Marie-Louise Newell
Faculty of Medicine
University of Southampton

26 November 2014

Re: Project 12542 PIMS

Dear Professor Newell

Thank you for submitting your revised application relating to this study. I am pleased to inform you that full approval has now been granted by the Faculty of Medicine Ethics Committee.

Approval is valid from today until 8 January 2018 which is the end date specified in your application. We will be in touch with you again in January 2018 to confirm that your project has been completed.

Please note the following points:

- the above ethics approval number must be quoted in all correspondence relating to your research, including emails;
- if you wish to make any substantive changes to your project you must inform the Faculty of Medicine Ethics Committee as soon as possible.

Please note that this email will now constitute evidence of ethical approval. Should you require a paper signed copy of this approval, please contact the FoMEC Administrative Team via email at: Medethic@soton.ac.uk. We wish you well with your research.

Yours sincerely

Dr Catherine Hill

Faculty of Medicine Ethics Committee

Please reply to:
Mrs Anne Tarrant
Faculty of Medicine Ethics Committee, Southampton General Hospital, Mailpoint 801, South Academic Block, Tremona Road, Southampton SO16 6YD United Kingdom

University of Southampton, Highfield Campus, Southampton SO17 1BJ United Kingdom
Tel: +44 (0)23 8059 2819 Fax: +44 (0)23 8059 3131 www.southampton.ac.uk

3. PARTICIPANT CONSENT FORMS

3A. Study Informed Consent Form for Entire Cohort (Assessment A)

PIMS: Informed Consent Form #1
English Version 1.0, March 2015

PIMS INFORMED CONSENT 1
GROUP 1 PREGNANCY CONSENT

WHAT IS THE PURPOSE OF THIS STUDY?
We are from the University of Cape Town and University of Southampton, UK. You are being asked to take part in a study that is being conducted at the Gugulethu Midwife Obstetric Unit (MOU). The purpose of this study is to understand how to improve health care services for women during their pregnancy.

You are being asked to take part in this study because you are a pregnant woman and you are getting your pregnancy care here at the Gugulethu MOU. The purpose of this consent is to give you information to help you decide if you want to take part in this study.

WHAT DO I HAVE TO DO IF I AGREE TO TAKE PART?
If you agree to take part, you will do the following at today's visit:

- Answer a short questionnaire about yourself and your health
- If it appears that you are still early in your pregnancy, we would like you to have an ultrasound scan to see how far along you are in pregnancy
- Based on this information, we may invite you to participate in further research

Review of medical records
As part of this study, we will also be looking at and taking information from your antenatal, obstetric, medical, and laboratory records. From these records, we are interested in learning about the pregnancy care you received as well as information about your delivery. If you are HIV-positive, we also want to learn about the HIV care and treatment that you received during your pregnancy and after you delivered. All data that we review and abstract is confidential and no participant names are recorded on study documents.

Contact for future study
After the completion of this visit, it is possible that we will contact you again at your next clinic visit to take part in additional studies like this one. At that time, you would be asked to review and sign another consent form. You can choose to not take part in these additional visits if you are asked.

WHAT ARE THE POTENTIAL RISKS?
If you decide to participate, you may feel uncomfortable about some of the personal questions you are asked about your health or your pregnancy. You may refuse to answer any question that you do not want to answer. There is some risk in sharing personal and medical information. We will be careful to keep all your information as private as possible.

WHAT ARE THE POTENTIAL BENEFITS?
There is no direct benefit to you if you take part in this study but if we identify any health care problem during the course of the study, we will make sure you are referred to the appropriate health care services. The information gained in this study may help to improve services for pregnant women in Cape Town, the Western Cape Province, and across South Africa.

WHAT ARE THE ALTERNATIVES TO TAKING PART?
The alternative to taking part in this study is to continue with your usual health care. If you decide not to participate in this study, your usual health care will not be changed in any way.

3B. Study Informed Consent Form for HIV-Infected Subset of Cohort (Assessment B)

PIMS: Informed Consent Form #2
English Version 1.0, March 2015

PIMS INFORMED CONSENT 2
GROUP 2 PREGNANCY AND DELIVERY CONSENT

WHAT IS THE PURPOSE OF THIS STUDY?

We are from the University of Cape Town and University of Southampton, UK. You are being asked to take part in a study that is being conducted at the Gugulethu Midwife Obstetric Unit (MOU). The purpose of this study is to understand how to improve health care services for HIV-positive women during their pregnancy and after they deliver the baby.

We know that it is important for their own health as well as the health of their baby, that HIV-positive women receive the HIV care and treatment that they need both during and after delivery. Information learned in this study will help us to improve HIV services for pregnant women.

You are being asked to take part in this study because you are a pregnant woman with known HIV infection who is taking HIV drugs (antiretroviral therapy) and you took part in the first part of this study. The purpose of this consent form is to give you information to help you decide if you want to take part in the next part of this study.

WHAT DO I HAVE TO DO IF I AGREE TO TAKE PART?

If you agree to take part, you will come in for up to 6 study visits. These visits will take place today while you are in the clinic, and then every 2 months until you deliver, within one week of delivering your baby and again when your baby is about 10 weeks and 6 months old. All of these study visits are separate from the usual clinic visits that you will have for your pregnancy and HIV care. Study visits can be timed so that they take place on the same days that you come in for your usual pregnancy and/or HIV care. The first visit today will take about 60 minutes and each of the subsequent visits will take about 30 minutes.

At the visits that are conducted *while you are pregnant*, you will do the following:

- Answer questions about your pregnancy and HIV-related health care and use of HIV drugs.
- Have your blood pressure, weight and height measured
- Have 6 tubes (50 mls) of blood drawn from your arm each time

One-week after delivery

One week after you give birth to your baby, you will come to the clinic for a visit that will include the following:

- Answer questions about your pregnancy and HIV-related health care and use of HIV drugs.
- Have your blood pressure, weight and height measured
- At this visit, we will ask you additional questions about your delivery, your baby's health, infant feeding and health care.
- Have 6 tubes (50 mls) of blood drawn from your arm.
- Have your baby's weight and height measured.

At the visits that are conducted *after your baby is born*, you will do the following:

- Answer questions about your recent health and HIV-related health care and use of HIV drugs.
- Answer questions about your baby's health, feeding practices and infant health care.
- Have your blood pressure, weight and height measured
- Have 6 tubes (50 mls) of blood drawn from your arm.
- Have your baby's weight and height measured

WHAT ABOUT CONFIDENTIALITY?
If you agree to take part, all information collected during the study will be kept strictly confidential. Your name will not be written on the study forms and will not be used in connection with any information or lab specimens that are collected as part of the study.

All study materials will be stored in locked filing cabinets. Only study staff and personnel involved in routine audits will have access to these materials. All staff involved in data collection and management will get specific training in confidentiality.

Even with these procedures in place, if the study staff learns that you are at risk of hurting yourself or someone else or of possible child abuse and/or neglect, study staff will tell the proper authorities.

WILL I BE GIVEN ANYTHING FOR TAKING PART?
No, there is no compensation for taking part in the study today.

ARE THERE ANY COSTS?
There is no cost for being in this study.

CAN I LEAVE THE STUDY?
You have the right to decide not to not take part in the study, to refuse to answer any questions, or to withdraw from the study at any time without any penalty. It will have no effect on the care that you receive at the Gugulethu MOU or any other health facility.

DO YOU HAVE ANY QUESTIONS?
If there is anything that is unclear or if you need further information, please ask us and we will provide it.
Do you have any questions?

FOR ADDITIONAL INFORMATION:
If you have any questions or have any problems while taking part in this research study, you should contact:

Prof Landon Myer
School of Public Health and Family Medicine
Faculty of Health Sciences
University of Cape Town

Tel: 021 406 6661
Email: Landon.Myer@uct.ac.za

Prof Marie Louise Newell
Human Development and Health Unit
Faculties of Medicine & Social and Human Sciences
University of Southampton, UK
Tel: +44 (023) 8059 3901
Email: m.newell@soton.ac.uk

If you have any questions about your rights as a research participant, you may contact the following member of the ethics committee:

Prof Marc Blockman, Chair
Human Research Ethics Committee
Faculty of Health Sciences, University of Cape Town
Tel: 021 406 6338

Dr Angela Fenwick, Chair
Southampton Faculty of Medicine Ethics Committee
Building 85, Life Sciences, Highfield Campus
Southampton SO17 1BJ, United Kingdom
Tel: +44 2381 208692

SIGNATURE PAGE

For participant to complete (please tick):

☐ I have read the information in this document (or it has been read to me). I have been offered a copy of this consent form. I was encouraged and given time to ask questions and all my questions about the study and my participation in it have been answered. I freely consent to be in this research study and agree to participate and know that I may withdraw at any time. My being in the study is voluntary. I understand that whether or not I participate will not affect my health care services received today, or at any time in the future.

☐ I agree that the study team can access my medical records at this hospital or another hospital if necessary for this study. My information will be kept confidential.

Participant Name (Please print)	Participant Signature	Date/Time

Interviewer Name (Please print)	Interviewer Signature	Date/Time

If this consent form is read to the participant because the participant is unable to read the form or if the participant must use a thumbprint to sign his/her name, an impartial witness not affiliated with the research or investigator must be present for the consent and sign the following statement:

I confirm that the information in the consent form and any other written information was accurately explained to, and apparently understood by, the participant. The participant freely consented to be in the research study.

Witness Name (Please print)	Witness Signature	Date/Time

Thank you

4. QUESTIONNAIRES AND DATA ABSTRACTION FORMS

4A. Maternal Demographics

PIMS: Demographics, Obstetric, Medical & ART History A1
Xhosa-English Version 2.2, 18th January 2016

MDOMA

PWID: _ _ _ _ _ _ - _ _

MATERNAL DEMOGRAPHICS, OBSTETRIC & MEDICAL HISTORY

This CRF applies to ALL enrolled Group 2 Participants
(HIV-infected & ≤20 weeks GA as confirmed by USS)
Complete during Enrolment (≤20 weeks) Study Visit

Visit Date								
D	D	M	M	M	Y	Y	Y	Y

Visit Code	
A	1

SOCIODEMOGRAPHIC INFORMATION	
1. Mingaphi iminyaka yakho *What is your age?*	*Age:* _____ Iminyaka *years*
2. Uzelwe Nini *What is your date of birth*	_____/_____/_____ DD MMM YYYY
3. Uthetha oluphi ulwimi ekhayai? *What language do you speak at home?*	☐ isiXhosa ☐ isiZulu ☐ isiBhulu *Afrikaans* ☐ isiNgesi *English* ☐ Olunye *Other* Cacisa *Specify:* _____
4. Leliphi elona banga liphezulu oliphumeleleyo? *What is the highest level of schooling/education that you have completed?*	☐ Umgangatho *Grade:* _____ Okanye *or* Ibanga *Standard:* _____ ☐ Imfundo enomsila *Postsecondary :* _____ ☐ None
5. Ngoku uyasebenza okanye uyafunda *Are you currently working and /or studying?*	☐ Ewe *Yes* ☐ Hayi *No* → **Gqithela ku Q7** **SKIP to Q7**
6. Ukuba nguEwe, yeyephi kwezi zilandelayo echaza, bhetele ukuba wenza ntoni? *If yes, which of one the following best describes what you do?* **Khetha ibenye** */Choose one only*	☐ Ndiphangela isigxina *Employed full-time* ☐ Ndiphangela mangqaphangqapha *Employed part-time* ☐ Ndiphangela izingxungxo /ndingumatheng'ethengisa *Informal job/hawker* ☐ Uhamba isikolo/ ungumfundi *Attending school/learner* ☐ Uhamba isikolo semfundo enomsila *Attending tertiary education facility*

7. Uhlala kwikhaya elinjani? *What kind of home do you live in?*			☐ Ityotyombe/ uhlaliso olungahlelwanga *Shack/informal dwelling* ☐ Indlu yesitena *Formal house* ☐ Ifleti/ indlu kamaspala *Flat/council home* ☐ Olunye *Other* Cacisa *Specify*: _____	
8. Ingaba indlu yakho inazo ezi zinto zilandelayo: *Does your house have the following:* **Phendula ZONKE** *Respond to ALL*	a. Indlu yangasese *A toilet inside*	☐ Ewe *Yes* ☐ Hayi *No*	b. Amanzi abalekayo empompo *Running water inside*	☐ Ewe *Yes* ☐ Hayi *No*
	c. Umbane *Electricity inside*	☐ Ewe *Yes* ☐ Hayi *No*	d. Isikhenkcisi *A refrigerator*	☐ Ewe *Yes* ☐ Hayi *No*
	e. Umnxeba *A telephone*	☐ Ewe *Yes* ☐ Hayi *No*	f. Umabona kude *A television*	☐ Ewe *Yes* ☐ Hayi *No*
9. Ukhulelwe kangaphi (kudibene nesi isisu)? *How many times have you been pregnant (incl. current pregnancy)?*			Inani lokukhulelwa: _____ *# of pregnancies:*	
10. Bangaphi abantwana obazeleyo? *How many children have you given birth to?*			Inani labantwana: ☐ _____ ☐ None *# of children* → **Ukuba awunabo abantwana, Gqithela ku Q12** *If NONE, SKIP to Q12*	
11. Bangaphi kwaba bantwana abaphilayo? *How many of these children are living?*			Inani labantwana: ☐ _____ ☐ None *# of children*	
12. Uya thandana ngoku? *Are you currently in a relationship?*			☐ Ewe *Yes* ☐ Hayi *No* → **Gqithela ku Q15**	
13. Ungaluchaza njani uthando lwakho? *How would you describe your current relationship?*			☐ Utshatile *Married* ☐ Anditshatanga ,ndiya hlalisana *Not married, living together* ☐ Nditshatile, asihlali kunye *Married, not living together* ☐ Anditshatanga, asihlali kunye *Not married, not living together* ☐ Olunye *Other* Cacisa *Specify*: _____	
14. Lileshe ellingakanani unobudlelwana nalomntu? *How long have you been in a relationship with this person?*			Ixesha *Duration in:* Inyanga *Months*: _____ Okanye *or* Iminyaka *Years*: _____	

4B. Maternity Case Record Abstraction Form

PIMS: Data Abstraction Form: Maternity Case Record
Version 2.0, 24th March 2016

MCRA

PWID: _ _ _ _ _ _ - _ _

MATERNITY CASE RECORD ABSTRACTION FORM

This form applies to ALL enrolled Group 1 Participants
Complete after conclusion of routine Antenatal Care Booking Visit Procedures

Date of Data Abstraction:	_____ / _____ / _____ DD MMM YYYY		**Initials of Data Abstractor:**		
Participant Full Name:			**Participant Date of Birth:**	_____ / _____ / _____ DD MMM YYYY	
Participant National ID			**Provincial Folder Number:** (specify 3 letter facility prefix: GUP or other)	G U P	
Gravidity		**Parity**		**Miscarriages**	

Previous Pregnancies (as per Maternity Chart)

Year	Gestation	Delivery	Weight	Sex	Outcome	Complications

Medical & General History

THIS Pregnancy **Healthy:** ☐ YES ☐ NO If NO tick all options that apply	☐ Hypertension ☐ Epilepsy ☐ Cardiac ☐ TB ☐ Other:_____ Further details if any of the above selected: _____ _____
Previous Pregnancies ☐ N/A	☐ Twins ☐ Diabetes ☐ TB ☐ Congenital ☐ Other:_____ Further details if any of the above selected: _____ _____

Details of Booking Examination

Date _____ / _____ / _____ DD MMM YYYY	**Clinic:** ☐ GMOU ☐ Other: _____	**# visits:**
BP _____ / _____ Systolic Diastolic	**HB** _____ g/dl	**Height:** _____ cm
Weight: _____ kg	**MUAC:** _____ cm	**SFH:** _____ cm

RPR Result	Neg	Pos	**Titre if pos:** _____	**Rhesus:** _____	**ABO Bloodgroup:** _____

1st HIV Test	___ / ____ / ____ DD MMM YYYY		**RESULT**			**2nd HIV Test**	___ / ____ / ____ DD MMM YYYY		**RESULT**		
			POS	NEG	Decline				POS	NEG	Decline
On ART	Y	N	**Initiation Date**	___ / _____ / ____ DD MMM YYYY		**Regimen**					

EDD Estimation

Date of assessment #1	___ / _____ / ____	**# 1: Type**	Date / LNMP	SFH	USS
Gestational Age (weeks):		EDD: ___ / ___ / ___ DD MMM YYYY			
Date of assessment #2	___ / _____ / ____	**#2: Type**	Date / LNMP	SFH	USS
Gestational Age (weeks):		EDD: ___ / ___ / ___ DD MMM YYYY			
Date of assessment #3	___ / _____ / ____	**#3: Type**	Date / LNMP	SFH	USS
Gestational Age (weeks):		EDD: ___ / ___ / ___ DD MMM YYYY			

Additional Notes:

If Referred: GMOU Visit Date _____ / _____ / _____ Reason for Referral:

4C. Obstetric Data Abstraction Form

PIMS: Data Abstraction Form: Obstetric Record
Version 3.0, 19th December 2016

PWID: _ _ _ _ _ _ - _ _ **ODA**

OBSTETRICS ABSTRACTION FORM

This form applies to ALL enrolled Group 1 Participants
Complete after delivery

Date of Data Abstraction:	_____ / _____ / _____ DD MMM YYYY	**Initials of Data Abstractor:**	
Participant Full Name:		**Participant Date of Birth:**	_____ / _____ / _____ DD MMM YYYY
Participant National ID		**Provincial Folder Number:** specify 3 letter facility prefix; GUP or other	G U P
Source Document	☐ Maternity Case Record ☐ Delivery Register ☐ PMTCT Register (incl DISA/Trakcare) ☐ Other, Please Specify: _____		

Mothers Details

Name of clinic			**GA at 1st visit**			**Booking Date**	_____ / _____ / _____ DD MMM YYYY	
Hb			**Rhesus**	Pos	Neg	**Syphilis**	Pos	Neg
HIV results	Pos	Neg	**HIV retest**	Pos	Neg	**ART**	Y	N
Regimen			☐ NR			**ART Start Date**	_____ / _____ / _____ DD MMM YYYY	
Estimated Gestational Age	Weeks:_____ If weeks not recorded: ☐ Term ☐ Preterm		**Gestational Age estimated by**	☐ Dates ☐ SFH ☐ Not Reported		☐ Palpitation ☐ Ultrasound Scan		

Blood Pressure Details

Any hypertension noted at any time before labour? *(Systolic Over 140 and/or Diastolic Over 90)*	☐ Yes ☐ No	**Were any hypertensives given during this period?**	☐ Yes ☐ No
Any hypertension noted during labour? *(Systolic Over 140 and/or Diastolic Over 90)*	☐ Yes ☐ No	**Were any hypertensives given during this period?**	☐ Yes ☐ No
Maximum Systolic BP (at any point in pregnancy) *Record complete measure*	_____ / _____ systolic diastolic	**Maximum Diastolic BP (at any point in pregnancy)** *Record complete measure*	_____ / _____ systolic diastolic
Date this BP was taken	_____ / _____ / _____ DD MMM YYYY	**Date this BP was taken**	_____ / _____ / _____ DD MMM YYYY

Labour Details

Delivery Date	_____ / _____ / _____ DD MMM YYYY			**Delivery time**	_____ : _____		
Fetal Heart	Present	Absent	uncertain	**Fetal Distress**	Y	N	NR
Place of Delivery	☐ GMOU ☐ MMH ☐ GSH ☐ Other, Specify: _____			**Delivery Method** *Please tick all methods used during this delivery*	☐ NVD ☐ C/S ☐ Induction of labour ☐ Vacuum ☐ Forceps ☐ BBA		

If C/S, Primary indication	☐ Fetal distress ☐ Obstructed labour ☐ Twins/Triplets ☐ Pre-eclampsia /eclampsia ☐ APH ☐ Previous C/S ☐ Other, specify: _____	**If by C/S, was it performed after membrane rupture?**	☐ Yes, Duration:_____ Mins ☐ No ☐ NR

Please tick all major medical and/or obstetric conditions the mother experienced during pregnancy and/or during delivery.	☐ Chorio amnionitis ☐ Sepsis ☐ UTI / Pyelonephritis ☐ IUGR ☐ Hypertension ☐ Pre-eclampsia/ eclampsia ☐ Diabetes mellitus ☐ Preterm labour ☐ APH ☐ PPH ☐ Prolonged ROM ☐ Prolonged labour ☐ Cervical tear ☐ Perineal tear ☐ Episiotomy ☐ Other, Specify: _____

Placenta method of delivery	☐ Active ☐ Spontaneous ☐ Manual	**Placenta**	☐ Complete ☐ Incomplete ☐ NR	Weight: _____ g

Infant Details

Infant DOB	_____ / _____ / _____ DD MMM YYYY	**Infant DOB for Twin B**	_____ / _____ / _____ DD MMM YYYY
Gender	☐ Male ☐ Female	**Gender Twin B**	☐ Male ☐ Female
Outcome	☐ Alive ☐ Stillborn ☐ NND	**Outcome Twin B**	☐ Alive ☐ Stillborn ☐ NND
Resuscitation	☐ Yes ☐ No	**Resuscitation Twin B**	☐ Yes ☐ No
Birthweight	_____ g	**Birthweight Twin B**	_____ g
Head circumference	_____ cm	**Head circumference Twin B**	_____ cm
Length	_____ cm	**Length Twin B**	_____ cm
APGAR Score	1 min: _____ 5 min: _____	**APGAR Score Twin B**	1 min: _____ 5 min: _____
Congenital Abnormalities?	☐ Yes ☐ No ☐ NR	**Congenital Abnormalities Twin B**	☐ Yes ☐ No ☐ NR
Polio Vaccine?	☐ Yes ☐ No ☐ NR	**Polio Vaccine Twin B**	☐ Yes ☐ No ☐ NR
BCG Vaccine?	☐ Yes ☐ No ☐ NR	**BCG Vaccine Twin B**	☐ Yes ☐ No ☐ NR
NVP at birth?	☐ Yes ☐ No ☐ NR	**Twin B NVP at birth?**	☐ Yes ☐ No ☐ NR
Feeding Option	☐ Breast ☐ Formula		

Discharge Summary

Family planning choice	☐ Oral contraceptive ☐ Injectable ☐ IUD ☐ Implant ☐ Tubal ligation ☐ Other: _____
Date of discharge	_____ / _____ / _____ DD MMM YYYY

4D. Maternal Physical Examination Form

PIMS: Maternal Physical Examination Form A1
Version 1.0, April 2015

MPE A1

PWID: _ _ _ _ _ _ - _ _

MATERNAL PHYSICAL EXAMINATION FORM

This CRF applies to ALL enrolled Group 2 Participants
Complete during Enrolment (≤20 weeks) Study Visit

Visit Date								
D	D	M	M	M	Y	Y	Y	Y

Visit Code	
A	**1**

ANTHROPOMETRY	
Height	☐☐☐.☐ cm ☐ Not Measured
Weight	☐☐☐.☐ kg ☐ Not Measured
MUAC	☐☐.☐ cm ☐ Not Measured
BLOOD PRESSURE	
Reading 1	**Time of Measurement** ☐☐:☐☐ **Systolic:** ☐☐☐ mmHg **Diastolic:** ☐☐☐ mmHg
Reading 2	**Time of Measurement** ☐☐:☐☐ **Systolic:** ☐☐☐ mmHg **Diastolic:** ☐☐☐ mmHg
Reading 3	**Time of Measurement** ☐☐:☐☐ **Systolic:** ☐☐☐ mmHg **Diastolic:** ☐☐☐ mmHg
	☐ Blood Pressure Not Measured → **END** **Method:** (tick one) ☐ Manual ☐ Automated **Location:** (tick one) ☐ Left Arm ☐ Right Arm **Position:** (tick one) ☐ Sitting ☐ Supine ☐ Standing

4E. Infant Clinic Card

DETAILS OF CHILD AND FAMILY (To be completed at birth)	
Child's first name and surname: _____	
Child's ID number: ☐☐☐☐☐☐☐☐☐☐☐☐☐	
Mother's ID number: ☐☐☐☐☐☐☐☐☐☐☐☐☐	
Date of birth / / dd mm yyyy	Name of facility where child was born:
Child's residential address:	
Mother's name:	Mother's birth date:
Father's name:	Who does the child live with?
How many children has the mother had (including this child?)	
Number born (including stillbirths) ☐	Reason(s) for death(s):
Number alive now ☐	Date information given: / / / dd mm yyyy
Child in need of special care (mark with X) (Complete at delivery or at first contact with health services)	
Is the baby a twin, triplet, etc? Yes ☐ No ☐	Does the mother need additional support to care for the child? (Specify) Yes ☐ No ☐
Any disability present (including birth defects?) (Specify) Yes ☐ No ☐	Other: (Specify)

NEONATAL INFORMATION		
Birth weight:	Birth length:	Head circumference at birth:
Gestational age (weeks)	Rh factor	Mother's RPR
Antenatal (Maternal history):	Intrapartum (including mode of delivery)	
APGAR	1 min	5 min
Neonatal problems: (identify high risk problems):		
Neonatal Feeding: ☐ Exclusive breast ☐ Exclusive formula		
Special care plan / input required (e.g. Kangaroo Mother Care) Specify:		
Post-discharge plan (if baby was admitted in a neonatal ward/premature):		

5. JOURNAL INSTRUCTIONS TO AUTHORS

5A. BMJ Open Formatting Guidelines

Research articles

Research submissions should have a clear, justified research question.

We strongly encourage you to register your study. Prospective registration is mandatory for any clinical trials. Acceptable registries for trials are clinicaltrials.gov along with those listed here. We recommend Prospero for registration of systematic reviews.

All articles should include the following:

- **The article title should include the research question and the study design**. Titles should not declare the results of the study.
- **A structured abstract** (max. 300 words) including all the following where appropriate (please note that for RCTs there is a specific CONSORT extension for abstracts):
  - **objectives:** clear statement of main study aim and major hypothesis/research question
  - **design:** e.g. prospective, randomised, blinded, case control
  - **setting:** level of care e.g. primary, secondary; number of participating centres. Generalise; don't use the name of a specific centre, but give geographical location if important
  - **participants:** numbers entering and completing the study; sex and ethnic group if appropriate. Clear definitions of selection, entry and exclusion criteria
  - **interventions:** what, how, when and how long (this can be deleted if there were no interventions)
- **Articles should list each author's contribution individually at the end**; this section may also include contributors who do not qualify as authors. Please visit the ICMJE website for more information on authorship.
- **Any checklist and flow diagram for the appropriate reporting statement**, e.g. STROBE (see below).
- **A patient consent form:** any article that contains personal medical information about an identifiable living individual requires the patient's explicit consent before we can publish it. We will need the patient to sign our consent form, which requires the patient to have read the article. This form is available in multiple languages.
- **A data sharing statement**, such as: "Technical appendix, statistical code, and dataset available from the Dryad repository, DOI: [include DOI for dataset here].

We recommend your article does not exceed 4000 words, with up to five figures and tables. This is flexible, but exceeding this will impact upon the paper's 'readability'. Supplementary and raw data can be placed online alongside the article although we prefer raw data to be made publicly available and linked to in a suitable repository (e.g. Dryad, FigShare). We may request that you separate out some material into supplementary data files to make the main manuscript clearer for readers.

We also recommend, but do not insist, that the discussion section is no longer than five paragraphs and follows this overall structure (you do

- **primary and secondary outcome measures:** planned (i.e. in the protocol) and those finally measured (if different, explain why) – for quantitative studies only
- **results:** main results with (for quantitative studies) 95% confidence intervals and, where appropriate, the exact level of statistical significance and the number need to treat/harm. Whenever possible, state absolute rather than relative risks
- **conclusions:** primary conclusions and their implications, suggest areas for further research if appropriate. Do not go beyond the data in the article
- **where applicable, trial registration:** registry and number (for clinical trials and, if available, for observational studies and systematic reviews)

- **An Article Summary, placed after the abstract, consisting of the heading 'Strengths and limitations of this study'**, and containing up to five short bullet points, no longer than one sentence each, that relate specifically to the methods. They should not include the results of the study.
- **The original protocol for the study**, as a supplementary file.
- **A funding statement,** preferably worded as follows. Either: 'This work was supported by [name of funder] grant number [xxx]' or 'This research received no specific grant from any funding agency in the public, commercial or not-for-profit sectors'. You must ensure that the full, correct details of your funder(s) and any relevant grant numbers are included.
- **A competing interests statement**. See the BMJ Author Hub for details on what to include as competing interests.

not need to use these as subheadings): a statement of the principal findings; strengths and weaknesses of the study; strengths and weaknesses in relation to other studies, discussing important differences in results; the meaning of the study: possible explanations and implications for clinicians and policymakers; and unanswered questions and future research.

Authors are encouraged to submit figures and images in colour – there are no colour charges.

We require that you upload your figures as separate files rather than embedding them in the manuscript.

At upload you will be asked to choose one general subject area that applies to your article – it will be published under this banner on the main table of contents. You will also be asked to select further subject headings to be used for the 'Browse by topic' section, and specific keywords for help with identifying reviewers.

Following the lead of The BMJ and its patient partnership strategy, *BMJ Open* is encouraging active patient involvement in setting the research agenda. As such, we require authors of Research Articles to add a Patient and Public Involvement statement in the Methods section. Please see more details above.

Title page

This is excluded for the journal *BMJ Quality and Safety* which operates triple-blind peer review.

The title page must contain the following information:

- Title of the article.
- Full name, postal address, e-mail and telephone number of the corresponding author.
- Full name, department, institution, city and country of all co-authors.
- Word count, excluding title page, abstract, references, figures and tables.

Keywords

Authors can usually opt to (or are required to) choose keywords relevant to the content of the manuscript during the submission process. This assists in the identification of the most suitable reviewers for the manuscript. The selected keywords should also be included in the abstract itself.

Manuscript Format

The manuscript must be submitted as a Word document (*BMJ Case Reports* and *Veterinary Record Case Reports* request that authors submit using a template which should also be in Word format). PDF is not accepted.

The manuscript should be presented in the following order:

- Title page.
- Abstract, or a summary for case reports (Note: references should not be included in abstracts or summaries).
- Main text separated under appropriate headings and subheadings using the following hierarchy: BOLD CAPS, bold lower case, Plain text, Italics.
- Tables should be in Word format and placed in the main text where the table is first cited. Tables should also be cited in numerical order.
- Acknowledgments, Competing Interests, Funding and all other required statements.
- References. All references should be cited in the main text in numerical order.

Figures must be uploaded as separate files (view further details under the Figures/illustrations section). All figures must be cited within the main text in numerical order and legends should be provided at the end of the manuscript.

Online Supplementary materials should be uploaded using the File Designation "Supplementary File" on the submission site and cited in the main text.

Please remove any hidden text headers or footers from your file before submission.

Style

Acronyms and abbreviations should be used sparingly and fully explained when first used. Abbreviations and symbols must be standard. SI units should be used throughout, except for blood pressure values which should be reported in mm Hg.

Whenever possible, drugs should be given their approved generic name. Where a proprietary (brand) name is used, it should begin with a capital letter.

Figures/Illustrations

Images must be uploaded as separate files. All images must be cited within the main text in numerical order and legends must be provided (ideally at the end of the manuscript).

Video: How to improve your graphs and tables

Colour images and charges

For certain journals, authors of unsolicited manuscripts that wish to publish colour figures in print will be charged a fee to cover the cost of printing. Refer to the specific journal's instructions for authors for more information.

Alternatively, authors are encouraged to supply colour illustrations for online publication and black and white versions for print publication. Colour publication online is offered at no charge, but the figure legend must not refer to the use of colours.

Detailed guidance on figure preparation

File types

Figures should be submitted in TIFF, EPS, JPEG or PDF formats. In EPS files, text (if present) should be outlined. For non-vector files (eg TIFF, JPEG) a minimum resolution of 300 dpi is required, except for line art which should be 1200 dpi. Histograms should be presented in a simple, two-dimensional format, with no background grid.

For figures consisting of multiple images/parts, please ensure these are submitted as a single composite file for processing. We are unable to accept figures that are submitted as multiple files.

During submission, ensure that the figure files are labelled with the correct File Designation of "Mono Image" for black and white figures and "Colour Image" for colour figures.

Figures are checked using automated quality control and if they are below the minimum standard you will be alerted and asked to resupply them.

Please ensure that any specific patient/hospital details are removed or blacked out (e.g. X-rays, MRI scans, etc). Figures that use a black bar to obscure a patient's identity are NOT accepted.

Tables

Tables should be in Word format and placed in the main text where the table is first cited. Tables must be cited in the main text in numerical order. Please note that tables embedded as Excel files within the manuscript are NOT accepted. Tables in Excel should be copied and pasted into the manuscript Word file.

Tables should be self-explanatory and the data they contain must not be duplicated in the text or figures. Any tables submitted that are longer/larger than 2 pages will be published as online only supplementary material.

References

Authors are responsible for the accuracy of cited references and these should be checked before the manuscript is submitted.

Citing in the text

References must be numbered sequentially as they appear in the text. References cited in figures or tables (or in their legends and footnotes) should appear at the end of the reference list to avoid re-numbering if tables and figures are moved around at peer review/proof stage. Reference numbers in the text should be inserted immediately after punctuation (with no word spacing)—for example,[6] not [6].

Where more than one reference is cited, these should be separated by a comma, for example,[1, 4, 39]. For sequences of consecutive numbers, give the first and last number of the sequence separated by a hyphen, for example,[22-25]. References provided in this format are translated during the production process to superscript type, and act as hyperlinks from the text to the quoted references in electronic forms of the article.

Please note that if references are not cited in order the manuscript may be returned for amendment before it is passed on to the Editor for review.

Preparing the reference list

References must be numbered consecutively in the order in which they are mentioned in the text.

Only papers published or in press should be included in the reference list. Personal communications or unpublished data must be cited in parentheses in the text with the name(s) of the source(s) and the year. Authors should request permission from the source to cite unpublished data.

Journals from BMJ use a slightly modified version of Vancouver referencing style (see example below). Note that The BMJ uses a different style.

BMJ reference style

List the names and initials of all authors if there are 3 or fewer; otherwise list the first 3 and add 'et al.' (The exception is the Journal of Medical Genetics, which lists all authors). Use one space only between words up to the year and then no spaces. The journal title should be in italic and abbreviated according to the style of Medline. If the journal is not listed in Medline then it should be written out in full.

Check journal abbreviations using PubMed

Check citation information using PubMed

Example references

Journal article

13 Koziol-Mclain J, Brand D, Morgan D, et al. Measuring injury risk factors: question reliability in a statewide sample. *Inj Prev* 2000;6:148–50.

Chapter in book

14 Nagin D. General deterrence: a review of the empirical evidence. In: Blumstein A, Cohen J, Nagin D, eds. Deterrence and Incapacitation: Estimating the Effects of Criminal Sanctions on Crime Rates. Washington, DC: National Academy of Sciences 1978:95–139.